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PANEL DISCUSSION ON HYPERTENSION*

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MODERATOR G. E. WAKERLIN: By hypertension is meant a sustained increase in blood pressure, both systolic and diastolic, which indicates that disease is present. Hypertension is a sign of disease, just as are fever and leukocytosis. It is a fairly common sign of disease, as it occurs in 20 per cent of persons over the age of 40 in the United States. Clinical hypertension is classified in two large groups: 1) hypertension of known cause, which accounts for about 5 per cent of cases, and 2) hypertension of unknown cause, which accounts for the remaining 95 per cent.

There are renal, neurogenic, endocrine, and cardiovascular (used in a special sense) causes of hypertension. The exact mechanism of renal hypertension is not known at present. Among the renal causes, are smooth-muscle tumors in the wall of the renal artery, which produce constriction similar to that produced with the Goldblatt silver clamp. Tumors of the renal parenchyma and, more commonly, glomerulonephritis and pyelonephritis sometimes give rise to hypertension. The hypertension associated with toxemia of pregnancy is considered by some to be on a renal basis. Recently, it was found that pyelonephritis in dogs is due to altered secretion of renin. Whether this is true for human beings is not known.

Neurogenic hypertension may result from increased intracranial pressure. There is some evidence that this is due to increased tonus of the vasoconstrictor nerves supplying the arterioles. Rare lesions of the diencephalon and the brain stem may also cause neurogenic hypertension.

Next are endocrine causes. Hypertension may occur as a result of pituitary basophilism, probably by a concomitant change in the adrenal cortex rather than through altered pituitary function. Adrenocortical tumors may cause

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hypertension. Although the mechanism is not known, it is possible that there is an increase in an unidentified adrenocortical steroid which has a marked pressor effect and minimal effects on salt and carbohydrate metabolism. Hypertension is sometimes due to pheochromocytoma. In this instance, the cause is definitely known to be increased secretion of epinephrine and norepinephrine (usually predominantly norepinephrine).

Hypertension from cardiovascular causes (used in a limited sense) includes that associated with coarctation of the aorta. This is the result of the increased resistance in the coarctated area. When the coarctation is in the upper abdominal aorta there is probably a renal factor. Rarely, hypertension may be observed in patients with myocardial infarction, probably as a result of alterations in the renal circulation due to increased venous pressure.

The basic pathophysiologic mechanism in essential hypertension is unknown. Early in the disease, the cardiac output, the blood volume, the elasticity of the arteries, and the viscosity of the blood are within normal limits. The hypertension is due to an increase in the peripheral resistance, which early in the disease results from increased tonus of the smooth muscle of the systemic arterioles. The primary question is, what causes the increased tonus of the smooth muscle of the arterioles?

Something is known about the pathophysiology of the complications of essential hypertension, which occur mainly in the heart, brain, and kidneys. Due to increased systolic and diastolic pressures, the left ventricle undergoes work hypertrophy. The coronary arterial supply tends to lag behind, and the cardiac reserve is reduced. The coronary arteries are more subject to atherosclerosis in hypertension than in normotension. These are the pathophysiologic factors basic to myocardial insufficiency and coronary thrombosis as complications of essential hypertension.

As for the brain, the cerebral arteries are especially thin-walled and are poorly supported in the Virchow-Robin spaces. In hypertension the cerebral arteries are more subject to atherosclerosis. These basic pathophysiologic factors account for the occurrence of cerebral hemorrhage and cerebral thrombosis in cases of hypertension.

Usually, renal function is relatively good when death occurs from cardiac or brain complications, intercurrent infection, or other causes. Some of these patients die of old age. In 8 to 10 per cent of cases, arterio- and arteriolo-necrosis develop; these processes include the renal vessels, and cause considerable reduction in renal function. These patients die in a state of renal insufficiency. So-called malignant hypertension may be present from the start, or it may be grafted upon the more benign or more slowly moving form of essential hypertension.

What do we know about the pathogenesis of essential hypertension? Heredity plays a role. If both parents have essential hypertension, at least 50 per cent of their children will have it also. Body type plays a role. Is essential hypertension a generic classification or a single disease? A majority of investigators believe that it is a generic classification, but in order to differentiate the various types, the pathogenesis of essential hypertension must be determined. A few believe that essential hypertension is a single disease entity with different mani-

festations in different organ systems. The pathogenesis is not known, but it is established that renal, neurogenic and endocrine factors are involved.

In these patients there is an increased plasma concentration of vaso-excitatory material (Shorr), which comes from the kidney. Altered renin secretion may play a part in pathogenesis, but this is far from proved.

Neurogenic factors may play a role inasmuch as sedatives, general anesthetics, and vasomotor-blocking drugs reduce the hypertension in some patients. Sympathectomy is tantamount to cure in 5 to 10 per cent of cases.

That there is an endocrine factor, particularly an adrenocortical factor, is suggested by the mild alterations in sodium metabolism. About 10 per cent of patients with essential hypertension have normal or nearly normal blood pressure when partaking of a low-sodium diet, and in a few patients with rapidly advancing essential hypertension subjected to complete adrenalectomy and minimal substitution therapy there is significant reduction in blood pressure.

Recently, it has been suggested that all three of these factors may act together to alter sodium ion metabolism and thereby cause an increase in the tonus of arteriolar smooth muscle.

Obviously, to learn the pathogenesis of essential hypertension, we must continue investigative work in the laboratory and clinic. Only when the pathogenesis is known will treatment become specific instead of empiric as at present.

Dr. Talso will talk on the criteria of hypertension in older patients.

DR. PETER J. TALSO: In discussing the problem of hypertension and age, it may be well first to focus attention on the older patient. In 1850 there were 1 million persons over the age of 60 years in this country, whereas in 1955 there were 14 million over this age. By extrapolating, in 1975 there will be about 21 million persons over the age of 60. My purpose in mentioning these figures is to demonstrate that as each year passes we have an older and older population. The problems of blood pressure that apply to the older age group thus grow larger rather than smaller as time goes on.

I should like to consider the definition of hypertension and to point out certain important diagnostic considerations that must be kept in mind at all times. We must differentiate between high blood pressure *per se* and hypertensive disease. At present, most of us accept the values established by the Insurance Underwriters who studied this problem in 1943 and made a statement to the effect that blood pressure exceeding 160/90 mm. Hg must be considered abnormal at any age. Using the value 160/90 as the upper limit for normal blood pressure, and recognizing that hypertensive disease carries with it a well-defined mortality resulting from congestive failure and from the increased incidence of myocardial infarction, as Dr. Wakerlin has pointed out, the geriatrician would expect the incidence of hypertension to be low in the older age group, because most persons with hypertension should have died from hypertensive disease before reaching old age. In reference to this matter, I should like to cite certain data relative to the occurrence of hypertension in older aged people.

Dr. Masters examined the blood pressure values in 15,000 persons and found that 39 per cent of those between the ages of 40 and 49 years had a blood pres-

sure higher than 140/90. The percentage was found to rise with each decade until the ages of 80 to 89 years, when 85 per cent had a blood pressure above 140/90. Why is it that more and more persons with high blood pressure readings are seen in an aging population? This is in contrast to the accepted concepts of mortality in hypertensive disease and suggests that as people grow older there is a normal tendency for the blood pressure to rise and that an elevated blood pressure is a benign occurrence in old age. This problem has also been studied from a different point of view.

Data obtained from a series of 790 necropsies in patients above the age of 60 years, performed at the Peter Bent Brigham Hospital, were reported in 1951. Fifty-five per cent of the males and 69 per cent of the females had a systolic blood pressure above 140. Thirty per cent of both males and females had a diastolic blood pressure above 90. Approximately 40 per cent of the patients whose blood pressure was above these levels had heart disease demonstrable at necropsy. The remainder were free of evidence of heart disease. Interestingly, in this series of 790 patients over the age of 60 years, there was not a single instance of malignant hypertension or of malignant necrotizing nephrosclerosis. Obviously, although the blood pressure tends to rise with age, the disease appears to be less severe. Older aged people seem to tolerate an elevated blood pressure better than younger persons. With these ideas in mind, it has recently been suggested that the limits for normal blood pressure should be revised upwards and the effects of age be considered in this evaluation.

Masters recently presented data with reference to the blood pressure values found upon examination of 74,000 persons. Some of these data were obtained by questionnaire and may be of questionable value; however, he deduced that the lowest levels of systolic and diastolic pressures at which a diagnosis of hypertension should be made in persons of 16 years was 145/90. With each decade, the lowest level indicative of hypertension increases so that at age 60 to 64 years a blood pressure of 190/100 represents the lower limit of hypertension. This value may be somewhat high, but the study emphasizes the fact that perhaps we should have a more liberal idea toward making the diagnosis of hypertension.

We all can recall patients with a systolic blood pressure of 160 or 170, who have had definite complications of hypertension. They have had changes in the eyegrounds and in kidney function, or have sustained strokes or other complications of hypertensive disease. This emphasizes the fact that we must differentiate between the presence of an elevated blood pressure and the presence of hypertensive disease. We have all seen persons with high blood pressure who have lived out a normal life expectancy despite the presence of the elevated pressure. On the other hand, it is not unknown for patients to have a normal blood pressure despite the presence of severe hypertensive disease. One of the most striking instances of this condition occurred in a patient I examined a number of years ago. On examining the optic fundi, the changes of malignant hypertension were evident. Her blood pressure, however, was 120/80. On further examination, it was learned that this patient had multiple myeloma, which had caused a fracture of one of her vertebrae with resultant transection of her spinal cord. The diag-

nosis of malignant hypertension was confirmed at necropsy. Thus, some patients with a normal blood pressure may actually have malignant hypertensive disease. A similar situation may occur in association with a stroke, myocardial infarction, congestive heart failure, a febrile illness, or the use of ganglionic-blocking agents, so that the presence of a normal blood pressure in the older aged person does not necessarily rule out the presence of hypertensive disease.

In closing, I should like to stress again the fact that the level of the blood pressure of itself does not necessarily make the diagnosis of hypertensive disease. Perhaps we as physicians should review our criteria for the diagnosis of hypertension and assume a more lenient attitude toward older aged persons, but apply more rigorous diagnostic criteria generally.

MODERATOR WAKERLIN: Next will be a discussion of the diagnosis of hypertension in older patients by Dr. Shick.

DR. RICHARD M. SHICK: The condition of older as well as younger hypertensive patients is evaluated on the basis of a carefully taken history, physical examination (including examination of the eyegrounds), and appropriate laboratory studies, in order to exclude the presence of a correctable etiologic factor and to determine the severity of the hypertensive disease.

The degree of severity of hypertension can best be assessed by examination of the ocular fundi. Hypertension, whether essential or secondary, may be classified into four groups on the basis of changes in the eyegrounds. In group 1, the changes consist of mild narrowing and sclerosis of the retinal arterioles. In group 2, the arteriolar narrowing and sclerosis are more pronounced and focal arteriolar constrictions are present. In group 3, hemorrhages and exudates are present, in addition to the arteriolar changes. In group 4, or malignant hypertension, there is papilledema in addition to retinopathy and arteriolar changes. This classification does not take into account the complications of hypertension, and hence appropriate studies should be carried out to assess the functional integrity of the kidneys, heart and brain.

The most common type of hypertension is called "primary" or "essential," which indicates only that the specific cause is unknown. There is considerable evidence that this form of hypertension is commonly familial or inherited; beyond this all is mystery, so far as cause is concerned. Another variety of hypertension which may be considered "essential" is the systolic hypertension associated with atherosclerosis. In this type the systolic pressure is high and frequently variable, whereas the diastolic pressure is usually normal or only slightly elevated. From the therapeutic standpoint, it is important to distinguish this form from the "primary" form of essential hypertension, in which the values for both systolic and diastolic pressures are above the accepted upper limits of normal, *i.e.*, 150 and 100 mm., respectively. In the latter, specific treatment usually is indicated. In the systolic type, treatment is neither indicated nor effective, because it is not feasible to treat "hard pipes."

In contrast to essential hypertension, there are cases of hypertension in which a specific cause can be established and a complete cure can be accomplished. Admittedly, such causes are relatively uncommon and are more likely to be found in younger patients.

However, the evaluation of the hypertensive patient, either young or old, is incomplete without exclusion of secondary causes.

Although the majority of patients with coarctation of the aorta die before the age of 40 years, this condition occasionally is observed in older persons. The blood pressure of patients with coarctation is high in the arms and normal or low in the legs. There are no specific symptoms of coarctation. The condition should be suspected in all cases of hypertension, and one should always palpate the abdominal aorta and femoral arteries. If pulsations are reduced or absent, one should look for other evidence of coarctation. The blood pressure should be determined in the legs as well as the arms, and the patient should be examined for pulsating intercostal arteries. A systolic murmur may be heard over the base of the heart and the upper part of the back, as well as over the intercostal arteries. Roentgenologic examination of the thorax may disclose absence or smallness of the aortic knob and notching of the inferior borders of the ribs. The electrocardiogram is not helpful. Much information can be obtained by studies of direct arterial blood pressure in the arms and legs. There may be other anomalies associated with coarctation, such as a bicuspid aortic valve with aortic insufficiency and patent ductus arteriosus, to mention only a few. My surgical colleagues have operated on patients as old as 50 years of age, with gratifying results.

Hypertension may be secondary to renal disease. Probably every patient with significant hypertension and without azotemia, regardless of age, should undergo urographic studies in addition to urinalysis and tests of renal function, as part of an evaluation of hypertension for which no specific cause is apparent. Bilateral renal lesions, such as diffuse nephritis or glomerulonephritis, pyelonephritis and polycystic disease, need no comment.

Unilateral renal disease may cause hypertension, and following removal of a badly diseased kidney the blood pressure may return to normal, provided the remaining kidney is unaffected. The most common unilateral renal lesions associated with elevated blood pressure are atrophic pyelonephritis and tuberculosis. Hypertension caused by unilateral renal disease seems no different, so far as course and complications are concerned, than essential hypertension. Although unilateral renal disease is an uncommon cause of hypertension, the possibility always should be considered.

Intrinsic renal arterial lesions as a cause of hypertension are rare. However, in some cases nephrectomy may be followed by complete disappearance of hypertension. Such lesions include atherosclerosis with thrombosis, embolism, and aneurysm, to mention only a few. Results of excretory urography may be normal in these cases, and the diagnosis made only by aortography. The latter may show obstruction or aneurysmal dilatation of the renal artery, with an avascular kidney. The question is, when should aortography be performed? Certainly this procedure is not advisable for all patients with hypertension. The sudden onset of elevated blood pressure after an attack of pain in the flank should make one suspicious of renal arterial occlusion or aneurysm, and warrants aortography.

Hypertension may be related to lesions of the adrenal cortex or medulla. In

many instances, surgical removal of the lesions or the involved adrenal gland may cure the hypertension.

Hypertension may be caused by a functioning tumor or hyperplasia of the adrenal cortex, and it is a fairly constant finding in Cushing's disease. Other clinical features include plethora and rounding of the face ("moon facies"), obesity of the trunk with cervicodorsal fat pads ("buffalo hump"), thin extremities, hirsutism, acne, thin skin with purplish striations, and a tendency toward ecchymosis. Laboratory findings include lymphopenia, eosinopenia, low levels of serum potassium and plasma chlorides, an elevated level of plasma carbon dioxide, impaired glucose tolerance, abnormal urinary excretion of adrenocortical steroids, and osteoporosis. Results of surgical removal of a tumor, when present, or of partial or total adrenalectomy, have been gratifying.

Primary aldosteronism is a newly recognized syndrome characterized clinically by periodic severe muscular weakness, intermittent tetany and paresthesias, polyuria, polydipsia, and hypertension. The characteristic biochemical alterations in the blood include low values for potassium and elevated values for sodium and carbon dioxide. The syndrome is caused by adrenocortical adenomas, and it may be cured by removal of such lesions.

A pheochromocytoma of the adrenal medulla may produce sustained hypertension which may simulate essential hypertension. Another manifestation of pheochromocytoma is paroxysmal hypertension which, in addition to periodic elevation of the blood pressure, is characterized by attacks of one or more of the following: headache, vertigo, anxiety, sweating, circumoral pallor, dyspnea, pain in the thorax or abdomen, nausea, vomiting, weakness, and tremor. During the attack the blood pressure (which between attacks is normal) rises to more than 200 mm. Hg systolic, and 110 mm. diastolic.

Every patient with sustained or paroxysmal hypertension of a significant degree should be tested for the presence of a pheochromocytoma, because surgical removal of such a tumor cures the hypertension unless the lesion is malignant and has metastasized. Several drugs have been used in screening or provocative tests. In our experience, Regitine has been the most reliable agent for a screening test in sustained hypertension, and histamine has been the most reliable agent for a provocative test in paroxysmal hypertension caused by pheochromocytoma. If the basal blood pressure is more than 170 mm. Hg systolic, and 110 mm. diastolic, a dose of 5 mg. of Regitine is injected intravenously; the result is considered positive if the systolic blood pressure decreases more than 35 mm. and the diastolic more than 25 mm. If the basal blood pressure is less than 170 mm. Hg systolic, and 110 mm. diastolic, a dose of 0.05 mg. of histamine base in 0.5 cc. of isotonic solution of sodium chloride is injected intravenously. Before histamine is administered, the response of the blood pressure to immersion of a hand in ice water is determined; this is known as the "cold pressor test." The result of the histamine test is considered positive if, after a brief decrease, the blood pressure rises at the end of two minutes above the value reached with the cold pressor test. Of 51 patients with proved pheochromocytoma seen by my associates and me, 2 were more than 60 years old and 13 were more than 50 years old.

In conclusion, I should like to emphasize the point that the diagnosis of hypertension in older as well as in younger patients is made by the use of a blood-pressure cuff. I have never been able to understand those who consider the sphygmomanometer to be an instrument of the devil and wish it had never been invented. Such an attitude apparently stems from the fact that in years past, nothing could be done for hypertension; thus the physician was frustrated when he found the blood pressure to be elevated, and the patient was terrified because of the anticipated consequences. Currently, much can be done for hypertension.

MODERATOR WAKERLIN: The next presentation will be on the medical management of hypertension in older patients by Dr. Joseph C. Edwards.

DR. JOSEPH C. EDWARDS: In view of the foregoing presentations, my remarks can be confined to the medical management of the process known as hypertensive disease, the etiology, classification and diagnosis of which have been discussed.

The first thing one should do before treating a patient is to be certain of the diagnosis. Dr. Shick has outlined the things that should be considered in every patient in whom an elevated blood pressure is found. This does not mean that every patient must undergo all of these procedures the first day, but certainly each should have a careful physical examination, history, and the described basic screening tests. A level of blood pressure readings should be obtained because, undoubtedly, the pressure is different at different times in the same patient; it may vary during the day; and it may be affected by the activities of different physicians. Once the diagnosis of essential hypertension is made, attention may be directed toward treatment.

In the older age group, the problem is not so acute as in the younger age group. It is in those below the age of 50 years that more often the so-called malignant or accelerated phase of hypertension is seen, which requires immediate treatment because of the possibility of serious consequences. However, patients in older age groups should be treated if there are systolic and diastolic pressure elevations that the physician believes to be of consequence. There is a group of older patients who have a pressure of 160/90 and for whom little need be done except to treat them symptomatically, reassure them, and use mild sedation. Care must be exercised, and reserpine should not be given without considering some of the dangers. Neither the Kempner rice diet, a low-sodium diet, nor a 1-gram sodium diet is given, as efficient drugs are available for treatment. It may be necessary to restrict sodium intake because of high blood pressure or heart failure, as sodium holds water in the tissues due to certain other conditions, particularly in older patients. If the systolic blood pressure is only moderately elevated, there is less need for drug therapy. However, if the blood pressure rises to 210/110 or more as the patient is followed, the problem may be more serious.

It has been reported that the average duration of life from the known date of onset of hypertension in younger age groups is twenty years; thus hypertension may run a fairly uncomplicated course. It may be associated with either slow or rapid progression of lesions. In the milder forms of hypertension, the systolic pressure may be in the neighborhood of 160 to 180 mm. Hg and the

diastolic, 100 to 105; at times, the blood pressure may be normal. In these patients, the level of blood nonprotein nitrogen or blood urea nitrogen is determined, and a phenolsulfonphthalein test should be performed.

In about half of 71 patients with mild to moderately severe hypertension, the pressure was well controlled with Rauwolfia derivatives. In the remainder, other drugs were used. In general, the pressure was from 160 to 180 mm. Hg systolic and 95 to 110 diastolic, and there was no progression of the disease. Not all patients, even in the younger age group, should be given Rauwolfia derivatives, because they may induce serious depressive tendencies and even suicidal trends. These drugs are now known to be less innocuous than at first thought. When there is a history of a major depression or some emotional instability, the patient must be watched carefully if he is given Rauwolfia or reserpine. If such therapy is uncontrolled, some of these patients may have to be admitted to mental institutions. Electric shock has been of help in reversing the effects of these drugs.

Some persons with elevated blood pressure may require no more than a thorough investigation and mention of the word hypertension with reassurance and emphasis on the optimistic life expectancy. However, if there is moderate hypertension and the blood pressure remains elevated, the classification is probably grade 2, unless the patient has been heavily sedated. Complications occur in 30 to 40 per cent of these patients; when present, they reduce the life expectancy to about three years. In such patients, reserpine (0.25 mg. once or twice daily) may be used. Reserpine may be given continuously in a dosage of 0.25 mg. twice daily. Rauwolfia as the whole root (Raudixin) may be used in a dosage of 50 to 100 mg. twice daily; or the alseroxylon fraction (Rauwiloid), 2 mg. twice daily. There are also other preparations. Hydralazine should be administered with care, because it may create or simulate the so-called collagen or lupus diseases (such as disseminated lupus erythematosus), with tender muscles and joints and sometimes fever and malaise. (There may be other alterations, such as liver damage, revealed by positive results with the cephalin flocculation test.) If these symptoms appear, hydralazine should be stopped immediately, as the condition may become irreversible under continued therapy. In patients in whom hydralazine is stopped as soon as these manifestations become evident to the physician, the symptoms disappear; however, the lupus erythematosus cell may be found for a time in the bone marrow in some cases.

The Rauwolfia derivatives and Veratrum and Veriloid preparations are beneficial in severe hypertension which is not controllable by ordinary measures such as sedation. Effective dosages of the Veratrum drugs produce some toxic symptoms, such as nausea and vomiting. Patients must be observed very carefully when receiving these compounds. With the advent of Rauwolfia preparations and ganglionic-blocking agents, it is no longer necessary to employ the nausea-producing Veratrum derivatives, except occasionally when other drugs have failed. Ganglion-blocking agents are of value if the hypertension already is in the "malignant" stage with azotemia (grade 4); most of these patients die within three years. When hydralazine is used, the dosage must be adequate—up to 500 mg. a day, or even higher for a while. Because of the danger of toxicity,

this level is not maintained and the dosage is gradually lowered to the smallest optimum amount.

Many workers are enthusiastic about the use of ganglionic-blocking agents to control blood pressure in severe hypertension. However, Smirk in New Zealand and Schroeder in St. Louis believe that hydralazine should be used along with other ganglion-blocking agents. Other investigators are conservative and say that the latter should be used only in the most malignant types of hypertension. In patients who have reached the accelerated phase, in whom there is no hope of keeping the blood pressure down, and in whom other benefits cannot be obtained without the use of ganglion-blocking agents, these agents may be used if proper caution is employed. (Those to be named here are included only after very careful study.)

When using ganglion-blocking drugs in a case of severe cerebrovascular, renal or cardiac disease, the patient should be observed in the hospital because of the danger of producing some other complication or dire result due to sudden lowering of pressure—for example, another cerebrovascular accident. In a patient with renal insufficiency, abrupt hypotension may be induced. The less toxic of these drugs can be used in outpatients, as they do not lower the pressure so precipitously. Most workers in the field of hypertension, in clinical centers at least, believe that it is always advisable to have these patients hospitalized when using ganglion-blocking agents. I believe that not only in a few older patients, but in those below 50 years of age, it is possible to use these agents without hospitalization, if the physician is willing to take the time to study the patients carefully and to know the pharmacologic action of each drug.

Ganglion-blocking drugs should not be used in uncooperative subjects. Unless the patient is intelligent, cooperative, willing to come in, and willing to submit to care and detailed attention during the first few months, these drugs should not be given. However, it is possible and practical, if proper precautions are employed, to avoid hypotension.

These patients can measure their own blood pressure, and it should be determined before taking each dose of drug. If faintness occurs, the next dose should be omitted; if faintness is transient and does not require that the patient lie down or sit, half the next dose may be taken. Some patients become accustomed to taking their own blood pressure and gradually gain confidence. However, particularly for working people, the expense and trouble entailed make it impossible to determine the pressure before each dose of medication. Therefore, such patients are usually seen every week in the office to check for complications, or every few hours if the patient is in the hospital. Once the dosage has been regulated, the patient usually fares well and need be seen less often.

Care must be exercised to guard against the sudden postural hypotension brought on by the use of ganglion-blocking agents. If they are absorbed too rapidly or in too large an amount, the blood pressure may reach a distinctly low level when the patient is standing, and he may feel faint or may actually faint. The patient must be told that he may feel worse during the first few weeks of treatment, but that later he will feel better. The use of this form of therapy

does not necessarily insure that the blood pressure will be brought down to the level of 140/90, but it will be brought down to a more normal level for the patient.

In older persons particularly, more care should be exercised, and hospitalization should be encouraged more than in younger persons. Older persons are likely to have more arteriosclerosis. Therefore, it would be wise to hospitalize the few patients above the age of 60 years in whom the hypertension is severe enough to warrant the use of ganglion-blocking agents.

Hexamethonium chloride was one of the first ganglion-blocking drugs, and many questions arose about its practical use. It was thought that it had to be given every four hours, because only 40 to 50 per cent was absorbed. Now, it has been almost replaced by pentolinium (Ansolysen), which belongs to the quaternary ammonium group. A dose of approximately 40 mg. is given every four hours, perhaps starting with 20 mg. for two or three times and then gradually increasing the dosage on the second or third day, in accordance with the blood pressure readings, until it is given four, five, or six times. The patient gradually becomes adjusted over a two-week period. Some patients are in the so-called accelerated phase of grade 4 hypertension, and have reduced renal function and eyeground changes. They will eventually require a dosage of 100 mg. or even 200 mg. four times daily. When the hypertension is on a renal basis with insufficiency, naturally the level of blood pressure will be higher.

Mecamylamine has the advantage of being almost totally absorbed, whether given intramuscularly, intravenously, or by mouth. The initial dosage is 1 mg. two or three times daily, increased gradually to 2.5 mg. three times a day, and sometimes to as much as 5 to 10 mg. three to four times daily. Its action lasts slightly longer than that of chlorisondamine dimethochloride (Ecolid), the average dose of which is 50 mg. twice daily. These drugs are prepared in tablet form for oral use, and are usually given every twelve hours. However, we have found it better to give less in the morning (about 25 mg.) and considerably more in the evening, or to give 12.5 mg. at noon and 25.0 mg. at night.

Hypertensive emergencies, that is, malignant hypertension with confusion, disorientation, marked papilledema in the eyegrounds, and cerebral edema, are seen infrequently in the older age group. In such cases, we may try Veratrum (Veriloid) intramuscularly, or reserpine (Serpasil) by vein, but these drugs have to be used cautiously. It must be remembered that ganglion-blocking agents are dangerous. If they are not used with great care, they may precipitate a shock-like state due to hypotension. Pentolinium (Ansolysen) may be given continuously parenterally in order to reduce blood pressure in stepwise fashion; the test dose is from 1 to 5 mg.

Veriloid or reserpine intramuscularly is occasionally successful in the toxemia of pregnancy—a disease of the younger age groups. Hydralazine (25 mg. intramuscularly) is also helpful if used for one to three days in such emergencies.

As Dr. Pickering has said in speaking before a recent meeting of the American College of Physicians (*Annals of Internal Medicine*)—we now possess the means to control blood pressure, if not to cure hypertension.

Although the patients receiving drug therapy have not yet been followed as long as those undergoing sympathectomy, Schroeder, Smirk, McMichael, and others have reported some increase in the lifespan of patients with severe malignant hypertension (accelerated phase) treated with ganglion-blocking agents and hydralazine. Schroeder and I have seen patients treated with hexamethonium (or some other blocking agent) and hydralazine for two years or more, in whom the blood pressure has remained normal although they are now receiving no therapy. Schroeder reported 10 such instances among 114 patients. Occasionally, reserpine alone will lower the blood pressure in severe hypertension, although in most instances combination with other drugs is necessary. In patients who initially had congestive heart failure (left ventricular) it sometimes becomes possible to discontinue digitalis after the blood pressure has been controlled by the use of ganglion-blocking agents.

MODERATOR WAKERLIN: The last formal presentation is on the surgical management of hypertension in older patients by Dr. Geza de Takats.

DR. GEZA DE TAKATS: I am not going to speak about the obvious aim of surgery in hypertension, whether in the aged or middle aged, that is, the relief of known causes of hypertension. Dr. Schick, particularly, has aptly and adequately described what happens when a pheochromocytoma is removed or one kidney is removed because it seems to be the cause of hypertension; and in other cases in which there is coarctation of the aorta, or an adrenocortical lesion.

The largest group of patients with essential hypertension are those 30 to 50 years of age who are gradually becoming worse. The place for surgery, obviously, is in patients whose disease is progressing so rapidly that neither dietary management nor the drugs that Dr. Edwards described can check its progress. The surgeon is in an enviable position, so to speak, because he can from time to time obtain biopsy specimens of the blood vessels and the kidneys and correlate the histologic findings with the clinical findings and with cardiograms. When neither diet nor drugs can do anything except keep the patient in a comfortable condition, and when there is encephalopathy, the question arises as to whether to advocate surgery. I believe that by operating on these patients early the disease can be dampened or at least arrested. In a first group, there is intermittent hypertension with early vascular damage. It has been thought unwise to interfere in such cases. Even if the patient has early vascular damage, it may still be in the reversible stage of hypertrophy. If the eyegrounds show grade 1 or 2 retinopathy, the case should be considered for surgery, since a vulnerable vascular tree has been demonstrated.

A second group is characterized by a rising diastolic pressure in a middle-aged hypertensive patient. To these I would add the patients who do not respond well to diet and drug therapy. One of the reasons surgeons are glad to have complete records of medical management is because we think that preliminary therapy should continue for three to six months.

A third group is represented by 3 patients who were referred to us during the past month, all of whom had papilledema and blood nonprotein nitrogen levels of 60 mg. per 100 cc. We know that they are likely to die within a month or

two. Moreover, if I operate on them, they are going to die, because the disease is rapidly progressive. For operation to be feasible in cases of malignant and premalignant hypertension, renal function must be adequate. Excretion of phenolsulfonphthalein should be at least 15 per cent in fifteen minutes. It has been necessary to make arbitrary rules and standards. No attempt should be made to push surgery too far. That is the reason for speaking of the irreversibility of the vascular changes in this group.

Every patient has an optimal blood pressure with which he can live comfortably. It is not necessarily a normal pressure. For instance, a patient with arteriolarsclerosis will not feel well with a blood pressure as low as 120/80; yet he will be in satisfactory condition and able to work with a pressure of 160/100—the level to which it will be reduced after surgery. For this reason, it is exceedingly difficult to say whether or not a patient has been relieved of hypertension after surgery. The criterion of a good result in the first group is the patient's ability to work eight hours a day with a pressure of 160/80 without medication. If he does not have to see his physician every week, he has definitely been benefited. The criterion is based on the functional level considered worthwhile in a patient, but this does not necessarily involve a normal blood pressure. In the second group, stabilization of the diastolic blood pressure at a lower level is the aim of operation. In the third group, there should be regression of the papilledema and improvement of subjective symptoms.

We are now working on a ten-year to fifteen-year follow-up of our operative results. Among the first 100 patients with hypertension operated on more than ten years ago, worthwhile results were obtained in 60 per cent. The patients had grade 2 or grade 3 hypertension, and the majority of the changes were vascular. These patients have gone back to work. This is a better result than with any other form of therapy.

We make arteriograms only when there is a possibility that an adrenocortical tumor may be present, or some change in renal function. Fatalities and paraplegias have been reported following arteriograms. If carried out with care by a team which does nothing else, the procedure is fairly safe.

Sympathectomy, the operation that we still favor rather than adrenalectomy (except when there is evidence of excessive adrenocortical activity), is not to be undertaken lightly. It should be performed only in well selected patients and only after dietary and drug therapy have been tried without success. It is a major procedure, in that it prevents the patient from carrying on his full occupation for six weeks—about the same length of time as after a coronary occlusion. However, as well as we can judge from a quarter-century of experience, the results in well selected patients compare favorably with those of any other type of treatment which has so far been used.

MODERATOR WAKERLIN: At this time I shall ask for discussion and questions. Will you please direct your questions to a particular member of the panel.

QUESTION: What is the effect on vasomotor tonus of repeated stress phenomena, and of excess histamine produced during such stress?

MODERATOR WAKERLIN: Any stress may increase vasomotor tone by virtue

of altered cortico-hypothalamic activity with resulting increased medullary vasomotor-center tonus. Increased sympathetic nerve impulses to the adrenal medulla augment the secretion of norepinephrine and epinephrine, with an additional constricting effect on the smooth muscles of the arterioles. Increased vasomotor tonus may produce renal vasoconstriction, which may activate renal pressor mechanisms. These effects are blocked to a considerable extent by ganglion-blocking agents.

QUESTION: I wish to direct a question to the surgeon on the panel. If the average life span of the hypertensive patient is twenty years after the diagnosis is established, how many of your surgical patients would have done just as well under medical supervision after five, ten or fifteen years?

DR. DE TAKATS: Very shortly, statistics will be available from Dr. Smithwick's clinic. We have also tried to answer this very difficult question. No two groups are alike, and patients of the same type as those operated upon are never available for controls. However, there is no question but that in hypertension of grades 3 and 4 the mortality has been greatly reduced among patients undergoing operation as compared to that in patients treated without surgery. Among patients with grade 1 or 2 hypertension, using the Mayo Clinic classification, there is no notable difference. In other words, if a patient simply has an intermittent vasomotor instability, the blood pressure may decrease after sedation and going to bed for a day or two. He may still have intermittent attacks of hypertension. However, that is not the kind of patient under consideration—unless there is retinal vascular damage. I mainly refer to patients who have a continuous diastolic pressure of 110 mm. Hg, with detectable myocardial damage and eyegrounds that show either hemorrhage or papilledema. In this type of patient, life is definitely lengthened by surgery.

MODERATOR WAKERLIN: I might add that recently there have been published extensive statistics from Sweden comparing the life spans of patients managed medically and surgically. According to these data, sympathectomy definitely lengthened the life span.

QUESTION: May I ask how many members of the panel smoke?

MODERATOR WAKERLIN: Dr. Edwards.

DR. EDWARDS: I do not smoke regularly—not for medical reasons, but because of a busy life and practice. Not being an inveterate smoker, it is a matter of not having time. Nicotine and tobacco smoking cause constriction, particularly of the peripheral vessels, and therefore we ask most patients with essential hypertension to refrain from smoking. We usually suggest that they try to eliminate smoking for a month. If they feel better and if their blood pressure is lower, they will usually not want to start again. That seems to be the best approach. Occasionally, patients will say that they have already stopped several times.

MODERATOR WAKERLIN: Dr. Talso.

DR. TALSO: Basically, I agree with Dr. Edwards. However, if the patient comes back at the end of a month without cigarettes and is obviously nervous and tense, it is much better for him to smoke because it relieves some tension. It is

an outlet for pent-up emotions or nervous tension. Such persons would be doing themselves a disservice to stop smoking.

DR. SHICK: I agree with what has been said. I believe the best way to settle the problem is to ask yourself what you would say when confronted with a patient with hypertension. What would you tell him? I would say that eliminating smoking has never hurt anyone.

DR. DE TAKATS: I agree. I haven't smoked for thirty years. The effect of tobacco, particularly on the peripheral vascular system, should be avoided. I advise against its use. Dr. John Homans once told me that if a patient really understood what happens as the result of smoking, there would be no difficulty. The patient is impressed by being shown that the blood pressure goes up within two seconds after starting to smoke. However, if there is diffuse arteriosclerosis in a patient who has smoked all his life, and if I am certain that nicotine does not raise the blood pressure, I will not deprive the patient of smoking. In a younger or middle-aged patient who still has flexible vessels that respond to stimulation, I advise against smoking.

MODERATOR WAKERLIN: I have observed a pronounced decrease in cigarette smoking among people who are in investigative fields of medicine. Some of the decrease may only be apparent, due to better ventilation in meeting rooms. Medical meeting rooms always used to be filled with tobacco smoke, and now the rooms are relatively free of it. After smoking for twenty-five years, I stopped smoking about ten years ago, when authentic information began to appear on the relation between cancer and cardiovascular disease (other than Buerger's) and smoking.

A SIMPLIFIED INTRODUCTION TO STEROID CHEMISTRY FOR THE CLINICIAN*

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INTRODUCTION

During the past decade the role of the steroid hormones has passed from that of being primarily a research oddity to becoming a major therapeutic tool in the hands of progressive physicians everywhere. Although much has been written for the physician concerning the therapeutic steroid preparations and their administration, little or nothing has been given him in a digestible form concerning the essential chemistry of this important family of physiologic compounds.

The average physician is not basically a biochemist and he likes his chemistry in "easy to take" doses. Nevertheless, certain basic information relating to the steroids is essential to an intelligent correlation of disease state, therapy and laboratory information. It is, therefore, the purpose of this paper to present in as simple language as possible consistent with the complexity of the subject, some of the basic principles of steroid nomenclature, chemistry and metabolism.

GENERAL PRINCIPLES

The steroid hormones are associated with that group of biologic organic compounds that are loosely grouped together under the term *lipids*. Lipids are defined as biologic compounds which have a greasy, oily or waxy consistency, and are relatively insoluble in water, but soluble in the so-called fat solvents such as ether, benzene, chloroform or acetone. Among the family of lipids are a large number of compounds that are derivatives of a complex organic ring-structure known as cyclopentanoperhydrophenanthrene (Fig. 1).

Compounds derived from this structure are called *sterids*. When there are one or more hydroxyl groups (OH) attached to this structure the compounds are then called *sterols*, and cholesterol is the best known example of this group. When there are one or more carbonyl (C=O) groups on the basic structure it is called a *steroid*.

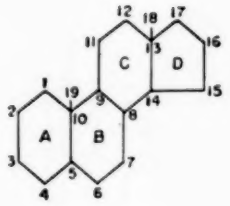
All of the steroid compounds may be considered to be derived from one of five basic sterid nuclei.

Thus all of the natural estrogens are derived from a sterid nucleus, estrane, containing 18 carbon atoms (Fig. 2). As a result, they are referred to as C-18 compounds.

Almost all of the natural androgens are derived from one of two sterid nuclei, androstane or etiocholane, each containing 19 carbon atoms (Fig. 3). The compounds in this group, therefore, are referred to as C-19 compounds. These two nuclei differ only in the sterio or optical position of the hydrogen atom extending from carbon atom number 5.

All of the corticoids, as well as progesterone and its derivatives, are derived

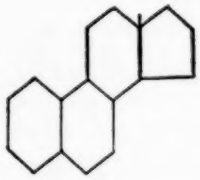
* Aided by a grant from The Wm. S. Merrell Company, Cincinnati, Ohio.



STERID NUCLEUS

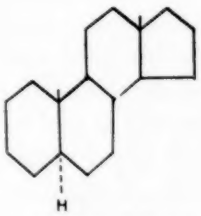
(CYCLOPENTANOPERHYDROPHENANTHRENE)

FIGURE 1

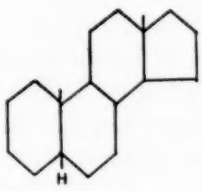


ESTRANE

FIGURE 2

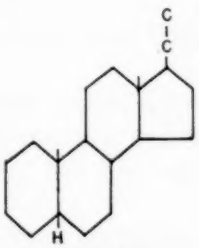


ANDROSTANE

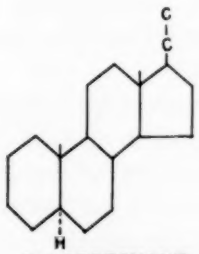


ETIOCHOLANE

FIGURE 3



PREGNANE



ALLOPREGNANE

FIGURE 4

from one of two sterid nuclei, pregnane or allopregnane, each containing 21 carbon atoms (Fig. 4). Consequently, members of this group are referred to as C-21 steroids. Again, as in the case of androstane and etiocholane, the nuclei differ one from the other only by the position of the C-5 hydrogen atom.

Each of the steroid compounds is named as a derivative of one of the foregoing five sterid nuclei. Common organic chemical suffixes and symbols are used to indicate changes and substitutions on the basic nucleus. The most important of these suffixes and symbols are as follows:

-ene a suffix to replace the -ane ending in the name of the nucleus when there are one or more double bonds in the ring.

Δ a symbol used to indicate the presence and location of a double bond in the ring.

-ol a suffix used to indicate the presence of an hydroxy or (OH) group.

-one a suffix used to indicate the presence of a keto or (=O) group.

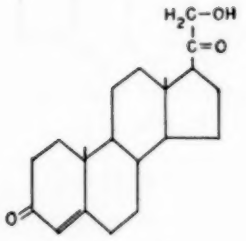
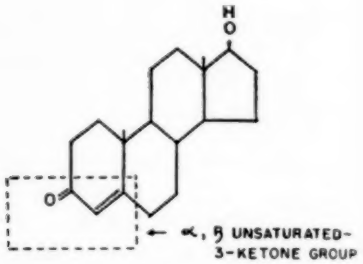


FIGURE 5



TESTOSTERONE

FIGURE 6

The use of these suffixes and symbols may be outlined with reference to the compound shown in Figure 5. This compound is a derivative of the sterid nucleus, pregnane. Since there is a double bond, we use the Δ symbol and change the *-ane* ending to *-ene*. Then a number is added to the Δ symbol to indicate the location of the double bond; since the double bond originates at carbon atom number 4, we use the symbol Δ^4. There is one hydroxy group, and it is on the carbon atom designated as number 21; therefore the suffix 21-ol is incorporated into the name. There are two keto groups, one on carbon atom 3 and one on carbon atom 20; consequently we use the suffix 3,20-*di*one (the *di* indicating two such groups). Thus the name of the compound illustrated is Δ^4-pregnene-21-ol-3,20-dione.

This set of simple rules may be used to derive the proper name of all of the steroids. The problem of common names and derived common names is somewhat different for each group of steroid compounds, and will be covered during the discussion of each particular group.

Although steroids are derived lipids and thus relatively insoluble in aqueous media, they appear in solution in the urine. This apparent discrepancy may be explained by the fact that the majority of steroids in the urine are not found in the free form but are conjugated with sulfate of glucuronide radicals, producing sulfate or glucuronide esters. Conjugation occurs at the number 3 carbon atom of the steroid nucleus. This carbon atom always possesses either an easily esterified hydroxy group or a keto group which may be easily converted into a hydroxy group. Many of the physiologically active steroids possess this 3-keto group instead of the 3-hydroxy group. Additionally, a double bond between carbon atoms 4 and 5 is very frequently found in these compounds. This particular structural combination is referred to as an α,β-unsaturated-3-ketone group and is typical of such physiologically active compounds as testosterone (Fig. 6), progesterone, cortisone or hydrocortisone. When this group is altered in any way, the activity of the particular compound diminishes considerably. Such alteration is obviously necessary in order to present a 3-hydroxy group for the formation of water-soluble conjugates, and thus we find that this type of deactivation frequently occurs in the metabolism of these compounds prior to their ultimate disposal in the urine.

THE C-18 STEROIDS (ESTROGENS)

In man, the naturally occurring estrogens are three in number. Although these compounds have proper names derived from the term estrane, they also have common names—estrone, estradiol and estriol (Fig. 7). The common names, however, give a clue to the structure of these compounds, and aid in cataloging them in one's mind. The *-one* ending in estrone indicates the presence of a keto group on the molecule, the *-diol* ending in estradiol indicates the presence of two hydroxy groups on the molecule, and the *-triol* ending in estriol indicates the presence of 3 hydroxy groups on the molecule.

The physiologic activity of these estrogens decreases as the degree of oxidation of the molecule increases. Thus estradiol, the least oxidized of the three, is the most active; estrone is next; and estriol is the least active.

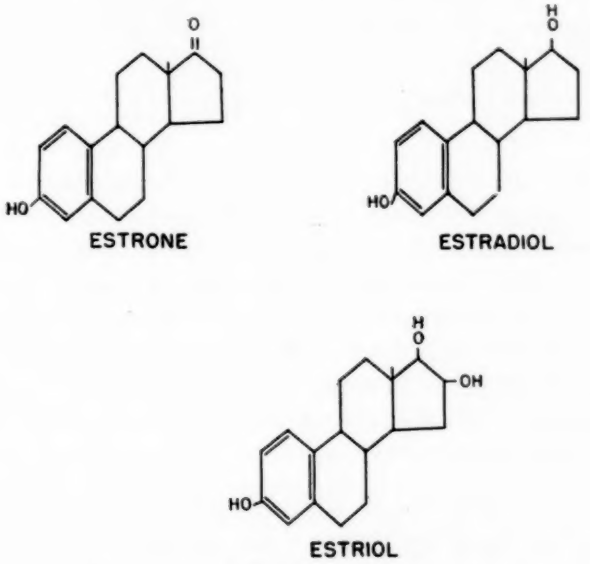


FIGURE 7

No chemical reaction is available for use in successfully assaying estrogens in the relatively crude urinary extracts obtained in a clinical endocrine laboratory, although certain specialized instrumentation techniques such as polarography have been reported as being of value. Estrogens are separated from the other steroids in a urinary extract by virtue of the fact that the phenol-like configuration of their "A" ring enables them to react with strong alkali to form water-soluble salts, which can be washed out of the extract. They are then measured by any one of several bioassays.

THE C-19 STEROIDS (ANDROGENS AND THEIR METABOLITES)

The C-19 steroids for the most part consist of the biologically active androgens of the adrenal cortex and testis, or their metabolites (some of which are active androgens and others of which are inactive). Some C-19 steroids found in the urine, however, are products of the degradation of C-21 steroids.

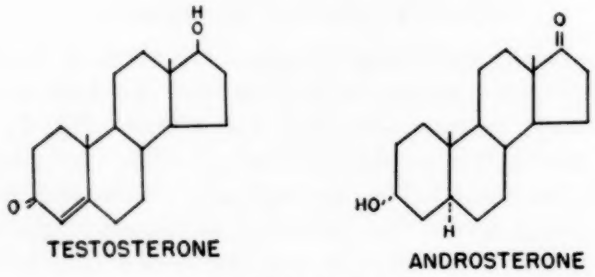


FIGURE 8

The problem of the common names of the C-19 steroids is not as complex as it may first appear. For two of these compounds—testosterone and androsterone (Fig. 8)—the common names are arbitrary. The remainder are named as derivatives of androsterone or of the basic sterid nuclei, androstane and etiocholane. The changes from the basic androsterone molecule in those compounds whose names are derived from androsterone are indicated by several chemical prefixes, these are:

epi or iso — these terms, which are used interchangeably in steroid nomenclature, indicate optical, or sterio, isomerism. As they are used here, they indicate a change in the 3-hydroxy group to the beta position. (In chemical usage, only the term "epi" is correct.)

dehydro — this term indicates the loss of 2 atoms of hydrogen from the molecule—one each from carbon atoms 5 and 6, resulting in a double bond between those two points.

hydroxy — this term indicates the presence of a hydroxy (OH) group somewhere on the molecule.

Keeping in mind the structure of androsterone, it may easily be seen how the two compounds represented in Figure 9 are named. For the compounds with common names derived from androstane or etiocholane, the changes in the basic molecule are indicated by the same set of chemical suffixes as are used in establishing their proper names. These suffixes (*e.g.*, -one, -ol, -ene,) are used, however, without numerical designation as to the position on the molecule where the

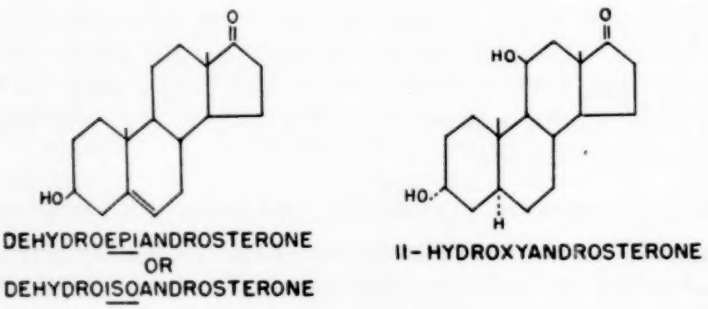


FIGURE 9

change occurs. There are several simple rules that may aid one in ascertaining the location of these structural changes:

1. There is always a keto group on carbon atom number 17.
2. If a double bond is indicated, it is between carbon atoms number 4 and 5.
3. There is always an oxygen-containing group on carbon atom number 3.

Thus it is easy to see, for example, that androstenedione is a molecule that differs from androstane, in that there is a double bond between carbon atoms 4 and 5, and there are keto groups on carbon atoms 3 and 17.

Testosterone is the only natural androgen of importance which does not possess a keto group on carbon atom number 17. Since testosterone as such is not found in the urine, but is metabolized to substances which have this 17-keto group, it follows that all of the important C-19 compounds in the urine possess a 17-keto group. For simplicity's sake, these substances are referred to as 17-ketosteroids. The 17-ketosteroids may be measured in the aggregate from relatively crude urinary extracts by means of the *Zimmermann reaction*. The Zimmermann reaction is the production of a pinkish purple color by 17-ketosteroids when they are treated with metadinitrobenzene in the presence of potassium hydroxide. This color may be compared quantitatively with the color produced by a pure steroid standard.

In certain cases of disturbed adrenal function it is sometimes important to fractionate the 17-ketosteroids into the so-called alpha and beta fractions. This is accomplished by means of the *digitonin precipitation* of the 17-ketosteroids in which there is a hydroxy group in the beta position on the number 3 carbon atom. That fraction which is precipitated with digitonin is called the beta fraction. The 17-ketosteroids that do not have a hydroxy group on number 3 carbon atom, and those in which there is an alpha-hydroxy group at that point, are not precipitated as digitonides and are referred to as the alpha fraction. The beta fraction has been found to be disproportionately elevated in most cases of adrenal tumor, and may be elevated also in congenital adrenal hyperplasia.

In order to obtain further information of this sort, a simple procedure for the measurement of dehydroepiandrosterone-like substances (which make up the major part of the beta fraction) has been developed. Known as the *Allen test*, it may be performed on the same total extract as the Zimmermann reaction. The test is based upon the fact that dehydroepiandrosterone and dehydroepiandrosterone-like substances produce a blue color when they are heated with a sulfuric acid-ethanol mixture and then diluted with additional ethanol after cooling. The reaction may be used qualitatively (since the presence of blue color indicates disproportionately high levels of dehydroepiandrosterone) or quantitatively (compared against a dehydroepiandrosterone standard).

THE C-21 STEROIDS. I. THE CORTICOIDS

The term corticoids is used to describe those C-21 steroids of the adrenal cortex that are involved in carbohydrate and/or salt and water metabolism. These compounds have one distinguishing structural feature which separates them from C-21 compounds which have other physiologic properties. This

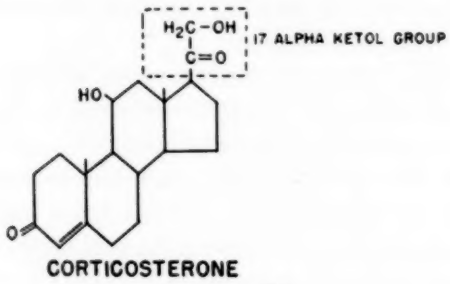


FIGURE 10

structural feature is known as the 17-alpha-ketol group (Fig. 10). This signifies that there is a two-carbon-atom side chain attached to carbon atom number 17 and that the first of these carbon atoms (C-20) possesses a keto group whereas the terminal one (C-21) contains a hydroxy group.

All the corticoids are given common names derived from the name of the compound illustrated in Figure 10—corticosterone. The structures of the steroids in this group differ only by changes at the sites of carbon atoms number 11 and 17. If, at carbon atom number 17, an hydroxy group is added to the basic corticosterone molecule, this change is indicated in the derived common name by the prefix *17-hydroxy*. At carbon atom number 11 there may be the usual hydroxy group which is found on the corticosterone molecule, but if this is changed to a keto group, the alteration is indicated in the derived name by the prefix *11-dehydro* (since the keto group may be produced from the hydroxy group by the loss of two atoms of hydrogen). If there is no oxygen-containing group at carbon atom number 11, the compound is designated by the prefix *11-desoxy*.

A summary of information which should be helpful in remembering the naming system of these important substances is listed in Table 1.

The physiologic properties of each of the corticoids are determined by the configuration at carbon atoms 11 and 17, according to the following general rules:

1. Oxygen, either in the form of an hydroxy group or a keto group, at carbon atom number 11 decreases the sodium-retaining properties of the molecule, and is necessary for regulation of carbohydrate metabolism.

2. An hydroxy group at carbon atom number 17 increases the carbohydrate-regulating activity of the molecule.

The C-21 compounds, in the course of their metabolism, tend to undergo fewer diversified structural changes than do the C-19 steroids. With the exception of a minor amount of degradation to C-19 compounds, these molecules are excreted in the urine in a form which allows identification of the physiologically active substances from which they originated. The major structural change which occurs during the metabolism of the corticoids involves the complete hydrogenation of the α,β-unsaturated-3-ketone group—a process which appreciably diminishes the physiologic activity of these compounds. Since such hydrogenation requires the addition of four atoms of hydrogen, these metabolic

TABLE 1

Compound	Common Name(s)	Substitution on No. 11 Carbon Atom	Substitution on No. 17 Carbon Atom
A	11-Dehydrocorticosterone	Keto (=O)	None
B	Corticosterone	Hydroxy (OH)	None
E	11-Dehydro-17-hydroxycorticosterone (cortisone)	Keto (=O)	Hydroxy (OH)
F	17-Hydroxycorticosterone (hydrocortisone)	Hydroxy (OH)	Hydroxy (OH)
Q	11-Desoxycorticosterone (desoxycorticosterone)	None	None
S	11-Desoxy-17-hydroxycorticosterone	None	Hydroxy (OH)

products are referred to as *tetrahydro compounds*. Thus cortisone, in the course of its metabolism, is converted to the excretory product, tetrahydrocortisone (Fig. 11).

Desoxycorticosterone is known to be metabolized primarily to pregnanediol. This metabolic compound is no longer a corticoid in nature, having lost the 17-alpha ketol group, but fortunately assay techniques are available for its measurement. In almost all other instances, except when there is a degradation to C-19 compounds, the 17-alpha ketol group remains intact during metabolism of the corticoids. Since this grouping is a distinguishing feature of the corticoids and remains intact in their metabolic products, the chemical tests for the identification and measurement of these compounds are based upon the reactions of this grouping.

Early assay techniques depended upon the reducing properties of the 17-alpha ketol group and involved the reduction of an alkaline copper solution or of phosphomolybdic acid, as in blood sugar determinations. Later, the so-called *formaldehydogenic corticoid* assay technique was developed. This depended upon the action of a strong oxidizing agent (periodic acid) in cleaving the 17-alpha ketol group between carbon atoms 20 and 21 and liberating a molecule of formaldehyde which was then distilled off and determined colorimetrically. Each mole of corticoid theoretically yielded a mole of formaldehyde.

Most of the corticoid assay techniques in use today in clinical laboratories measure the so-called *17-hydroxycorticoids* by the *Silber-Porter* reaction. This

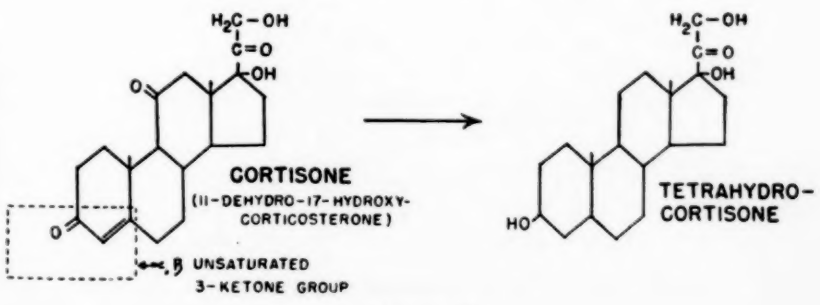


FIGURE 11

method is based upon the formation of highly colored compounds when phenylhydrazine in acidic solution reacts with steroids having the 17-alpha ketol group plus a 17-hydroxy group. Not all corticoids react in this manner, but fortunately the major ones do. Thus the method can be used for the determination of 17-hydroxycorticosterone (compound F or hydrocortisone), 17-hydroxy-11-dehydrocorticosterone (compound E or cortisone), and 17-hydroxy-11-desoxycorticosterone (compound S).

Occasionally one sees the term 11-oxycorticoids used in connection with a corticoid assay method. This usage dates back to an assumption by some workers that when a urinary extract is partitioned between benzene and water the 11-oxygenated steroids concentrate in the aqueous phase. Subsequent workers failed to confirm this assumption. However, there may be some justification for use of the term in procedures in which this partition is performed. Unfortunately, the term has become generally misused to denote some types of crude urinary extracts in which this separation method was not employed; in these cases its use is wholly without justification.

THE C-21 STEROIDS. II. PROGESTERONE AND ITS DERIVATIVES

The system of nomenclature for the common names of progesterone and its derivatives is very similar to that for the common names of the C-19 compounds. Progesterone is an arbitrary common name. One C-21 compound, 17-hydroxyprogesterone, is named as a derivative of progesterone. The remainder of the members of this group are named as derivatives of the sterid nucleus, pregnane, with the use of suffixes such as -ol, -one or -ene to indicate structural changes.

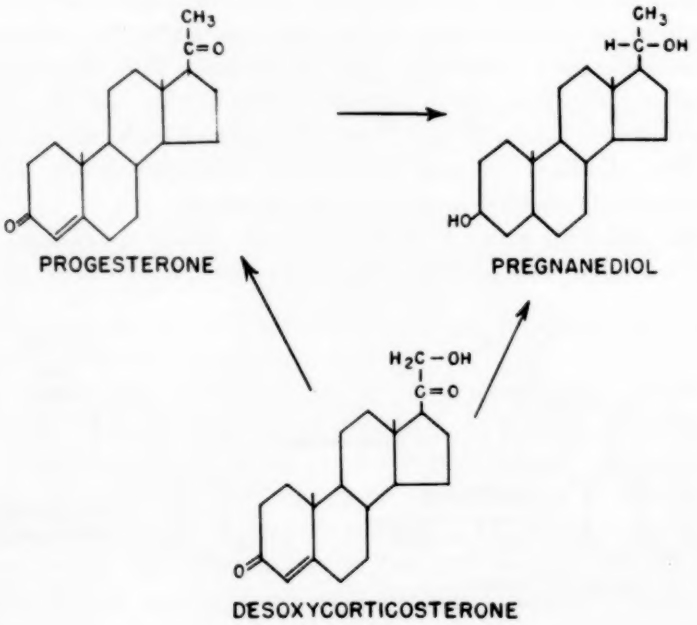


FIGURE 12

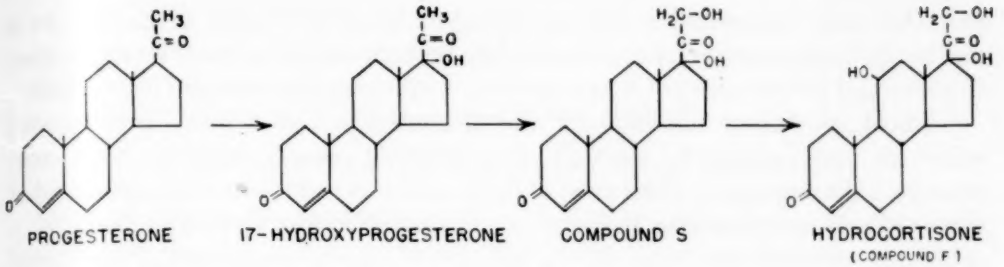


FIGURE 13

Again, as in the case of the C-19 steroids, numerical designations are not used in these derived common names to indicate the location of these changes.

Progesterone is mainly metabolized to one urinary derivative, *pregnanediol*. One of the corticoids, desoxycorticosterone, is also metabolized to pregnanediol (Fig. 12). The fact that desoxycorticosterone is metabolized to pregnanediol accounts for the presence of small amounts of this compound in the urine of males, of anovulatory females, and ovulatory females during the first phase of the cycle.

It is believed that progesterone is produced not only by the corpus luteum, but by the adrenal cortex as a precursor to the formation of 17-hydroxycorticosterone (compound F), one of the major corticoids in man (Fig. 13).

Since the foregoing reactions are catalyzed by specific enzymes, the lack of the proper enzyme or the presence of an inhibitor to that enzyme may stop the synthesis at any intermediate point. This defective synthesis is believed to occur in some types of congenital adrenal hyperplasia, due to either inhibition or lack of the enzyme 21-α-hydroxylase. Lack of this enzyme may prevent the process by which 17-hydroxyprogesterone becomes compound S and subsequently, hydrocortisone. Hydrocortisone is known to inhibit the production of corticotropin (ACTH) by the pituitary. Thus lack of hydrocortisone may permit an excessive production of ACTH with a resultant increase in the production of androgenic steroids by the adrenal cortex. Moreover, 17-hydroxyprogesterone is itself known to be mildly androgenic.

Since 17-hydroxyprogesterone is analogous to progesterone, and since enzyme systems exist for the metabolism of progesterone to pregnanediol, it might be assumed that the metabolism of 17-hydroxyprogesterone follows the same course

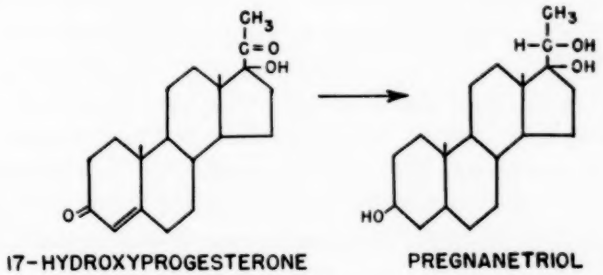


FIGURE 14

and that this compound would be excreted as *pregnanetriol* (Fig. 14). As a matter of fact, pregnanetriol excretion has been found to be considerably higher than normal in the urines of many patients with congenital adrenal hyperplasia.

Clinical laboratory methods for the determination of urinary pregnanediol which do not specifically separate pregnanetriol usually measure both compounds in the aggregate. Thus most of these methods yield values for pregnanediol which closely approximate the sum of the two steroids. Recently, however, a simplified method has been developed which allows pregnanediol and pregnanetriol to be separated from each other by adsorption chromotography on an alumina column, thus permitting individual determination of each compound.

VISUAL DIFFICULTIES IN OLDER PATIENTS

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Although serious eye disorders may develop in any decade of life, in general the incidence increases steadily as we grow older. The picture is not all black, however, since certain diseases which lead to loss of vision are less common in old age than in younger people. This is true in general of the inflammatory disorders such as iritis, uveitis and choroiditis. Loss of vision from injury is uncommon in older people, doubtless due to a more sheltered life and more restricted activities. Detachment of the retina is less common after the age of 65 than in the two or three decades preceding.

The principal causes of serious impairment of vision in older patients are glaucoma, cataract, and degenerative changes in the retina.

GLAUCOMA

There are two main types of primary glaucoma which, to oversimplify, may be divided into an acute and chronic form. Acute glaucoma, as the name implies, has an acute fulminating onset. It may develop in fullblown form within an hour. Characteristically the patient complains of marked visual loss, severe pain in or over the eye, and nausea and vomiting. Examination of the eye reveals more or less redness, more or less clouding of the cornea, and a partly dilated pupil which reacts little if at all to light. As compared to the other eye, the affected eye feels hard upon palpation. An acute attack may be precipitated by emotional upsets or by physical trauma. Acute glaucoma may be mistaken by the general physician for conjunctivitis or other benign disorder, and so treated; or, since the presenting symptom may be nausea and vomiting and general prostration, this symptom may be treated without realizing that the cause lies in the eye. When such a patient is finally referred to the ophthalmologist, it may be too late to save vision. The semidilated unreactive pupil is the most reliable sign of acute glaucoma.

A less violent form of acute glaucoma is often seen, in which the attacks of elevated tension are less severe. In the early stages there is usually spontaneous recovery. During an episode, the patient characteristically complains of blurred vision, ocular discomfort and seeing colored haloes about lights. These attacks are often precipitated by watching moving pictures or television or driving at night—probably due to pupillary dilatation in dim light. Between attacks the eye may return fully to normal. However, any patient who gives a history of periodic ocular discomfort with blurred vision and seeing colored haloes about lights deserves careful study by an ophthalmologist.

In a predisposed patient, systemic administration of atropin or an allied drug

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may precipitate an attack. Likewise an acute illness of any sort, or a general surgical operation may be the precipitating factor.

Chronic glaucoma, especially in older people, usually causes no symptoms until it is well advanced and there is considerable loss of vision. It can be detected by inspection of the optic disc with the ophthalmoscope and by measuring the tension of the eye. The general physician, if he uses the ophthalmoscope routinely, can easily learn to recognize glaucomatous cupping of the disc. The best plan for the early detection of chronic glaucoma is routine examination of all older patients' eyes by a capable ophthalmologist, every one to two years. Chronic glaucoma may coexist with other degenerative diseases, such as cataract and retinal degeneration. Glaucoma of all types tends to run in families. If one member of a family is known to have glaucoma, the siblings should have a thorough examination of the eyes at least once a year.

CATARACT

Any opacity in the lens may technically be termed cataract, yet not all cataracts result in blindness or even serious impairment of vision. Hence the term cataract should not automatically connote blindness. I dare say a very high percentage of people after 70 show more or less opacity of the lenses. A relatively small percentage of these opacities progress to the point where operation is required.

Opacities may commence in the anterior portion of the lens, in the nucleus or in the posterior portion. Having observed these types over a long period of years, the ophthalmologist can in the average case make fairly accurate predictions as to the future progress of the opacity. For instance, if it is confined to the anterior cortex of the lens, twenty or thirty years may elapse before serious impairment of vision takes place. Therefore, if this type of opacity first develops in the 60's, operation will rarely be necessary. Nuclear opacities usually exist for ten or twenty years before there is sufficient loss of vision to require operation. Posterior cortical opacities, on the other hand, usually progress much more rapidly. In some cases, operation may be required within two or three years after onset. Thus, depending on the type and location of the lens opacity, one patient can be dismissed with complete reassurance, whereas another must be prepared for the inevitable operation.

Operation can be carried out at any time if vision in the better eye has fallen sufficiently to handicap the patient seriously. Age is no contraindication; no one is too old to have a cataract operation if he is able to be up and about. Practically no systemic disease is a contraindication, provided there is a life expectancy of at least a few months. We ophthalmologists neither expect nor require general physicians to cure all the systemic diseases of old age before we are willing to undertake a cataract operation when it is indicated. The one requirement is the earnest desire of this old patient to see again. The wishes of other members of the family are not to be considered, for or against operation. It is the patient himself who must decide. Some older patients with greatly impaired vision are perfectly happy to continue as they are and do not want operation. They had

better be left alone and not urged, for under these circumstances they may not put enough spirit into it to survive the procedure. On the other hand, if the patient earnestly desires operation, he should have it, irrespective of the wishes of sons or daughters or other relatives who are not themselves suffering from the blindness.

DEGENERATIVE CHANGES IN THE RETINA

Degenerative changes in the macular region of the retina are so common in older people as to be considered a normal accompaniment of the aging process. These degenerative changes may sometimes occur in the 50's and 60's. They are very common in the 70's, and occur in a very high percentage of patients in the 80's. In the 90's, all are affected to a greater or lesser extent. Senile degeneration of the macular region of the retina takes many forms. Visual impairment varies from a slight degree to complete loss of central vision. The degenerative change is always confined to the macular region of the retina, and hence never results in total blindness. All reading vision may be lost, but the peripheral retina is unimpaired and the patient maintains "getting around vision."

There is no close correlation between the degree of generalized arteriosclerosis and senile macular degeneration. Macular degeneration often runs in families, and there is considerable evidence that it is genetically determined. There is no effective treatment at present. Various magnifying devices may be employed to provide some degree of reading vision, if the degenerative process is not too advanced.

MISCELLANEOUS

There are many other causes of visual impairment in older patients—for example, optic atrophy, or vascular disease in the retina or central nervous system. Diabetic retinopathy (proceeding at times to total blindness from retinal detachment and glaucoma) is a serious problem, but probably to a lesser extent in old age than in middle age. The factor or factors in diabetics which result in these serious eye disorders is still unknown and no effective treatment has, as yet, been devised.

SUMMARY

Though nothing can be done for eye disorders which are on a degenerative or arteriosclerotic basis, these conditions seldom lead to total blindness. Glaucoma, if diagnosed early and properly treated, can be controlled in most cases. Cataract is the least serious of all the disorders of the eye in old age. If advanced enough to cause serious impairment of vision, operation can always be performed, and the overall results are excellent.

DISPLACING THE OLDER PATIENT*

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When an inventory of patients is taken by any general practitioner who has been in the active practice of medicine for the past half-century, he finds that the sum total of his patients' ages has increased significantly, and that he is able to make observations on matters that he disregarded in the earlier days of his practice—a time when the reactions of his aged patients made little impression on him. Today, in like manner, the reactions of the aged are often unrecognized by the younger members of the profession, to the detriment of the patient.

During the past decade, increasing interest has been focused on our older people, brought about by the increased number of persons in our population who are over 65 years of age—the generally adopted age of retirement. Statistics reveal that the proportion of people who are 65 years of age and over has within recent years increased from 2 per cent to almost 8 per cent, and that there are now living in the United States 11 million persons in this age group. The Metropolitan Life Insurance Company estimates that by 1980 this number will be doubled—22 million.

In man, as in all animal and plant life, aging is a natural process and should, as such, be accepted by the patient and recognized and treated by the physician. With the young person, our aim is to make the most healthy, the most perfect, and the most useful individual possible with the material at hand. With the aged, on the other hand, our effort is to maintain and preserve that which in youth we created, and to make the inevitable aging more pleasant or tolerable. The process of aging is little understood, and the causes of the diseases of old age are in a large measure unknown. These diseases are insidious and chronic, and there are no short-cuts, vaccines or immunizations for their prevention. However, there are certain rules and principles which, if followed, will provide comfort and add years to the usefulness and happiness of our aged patients.

CHARACTERISTICS OF AGING

All animals and even plants are moulded by habit, and as they advance in life become ever more strongly rooted in their environment and fixed in their behavior. We all know how easy it is to transplant a young tree and have it thrive in its new location, and how extremely difficult and often impossible it is to transplant that same tree and have it live after it has reached maturity. We also are aware that young animals may be removed from their normal habitat and environment (even from the jungle to captivity) without greatly interfering with their normal life or life expectancy, and how extremely difficult it is for an older animal to adjust itself and live. We find by observation that man reacts no differ-

* Read by title at the Annual Meeting of the American Geriatrics Society, Chicago, Illinois, May 3 and 4, 1956.

ently than do plants and animals. During his development and maturation he forms certain habits and makes adjustments physically and mentally that become a part of his life, influencing physiologic function and even anatomic structure. Disruption of these acquired functions, or a displacement of the person, proves as harmful and destructive as it does in older plants or animals.

Much has been said and written about the compulsory retirement at age 65, the displacement of older by younger men, and the effect of this retirement on our economy. It appears that this early retirement will soon be more than the younger generation can bear, and that it is not in the interest of the older generation. However, this problem is not within the province of this presentation and must be left for solution to our economists. It is our purpose to call the attention of the practitioner of medicine and especially of the general practitioner to certain problems that confront him frequently, and the decisions that he is compelled to make in his care of these older people. To maintain the environment of younger days is the greatest problem of advancing age for the individual, for his family, for his physician, and for society at large. It is becoming ever more difficult of solution, but present economic and social conditions are bringing it into the foreground.

The older the individual, the harder it is for him to accept displacement and make adjustment. If progress is to continue, displacements must occur. As the individual grows older, he must relinquish certain prerogatives as well as duties. Nevertheless, present economic and social conditions often force the aging person into retirement and changes of life that are detrimental to health, well being, and life. The retirement age in industry, and migration from farm to city, have brought great harm to many people by depriving them of earning capacity, and even more by removing them as useful units of society and thereby destroying their morale and self respect. This is true more in our male than in our female population. Women are in this respect in a much more favorable position than men. It appears that they are always able to find some useful occupations that will keep them busy and happy, whereas the men often find themselves displaced, useless and thereby depressed—a condition which contributes to their earlier demise and shorter life expectancy.

The older the man the more fixed he becomes in his habits, his daily routine, and his likes and dislikes. He is accustomed to certain foods prepared in a certain way and certain hours of rest. He prefers the water of the old cistern or well, and no other quenches thirst as satisfactorily. These may appear to be minor considerations to the physician or nurse, but to many older patients they spell the alternatives of satisfaction or discontent, comfort or misery, means of recovery or continued decline and death.

HOME VERSUS HOSPITAL CARE

Among all nations in which men and women have studied the welfare of the aged, they have concluded that aged people fare better and are happier in their own homes in accustomed surroundings than in institutions, and should not be disturbed until all available means have been exhausted in an effort to keep them

in their homes. When hospital treatment is required, the patient recovers more rapidly if returned to his home as soon as possible. Many of our most modern treatments and tests can be carried out in and from the home as efficiently and as economically as in a hospital, and the extra time spent by the physician in directing treatment and securing specimens in the home will in most cases be compensated by the gratefulness of the patient and relatives.

Our visiting nurse's service has done much toward making home care more satisfactory and should be employed more frequently than at present.

To enumerate the many conditions, disabilities, and diseases for which home care is to be preferred to hospital treatment would make this presentation too lengthy. The extent of home care depends mainly on the willingness of the attending physician to serve the best interest of the patient even if it entails a sacrifice of personal convenience, and on the co-operation of the patient's family. In our present "set-up" in the practice of medicine the physician often finds it most difficult to apply modern methods of treatment and at the same time maintain the patient in accustomed surroundings and mode of living. Excellent judgment is required on the part of the attending physician to decide how far to proceed in either direction in order to do the least harm and secure the most benefit by treatment.

A study of the course of illness in the aged shows that, unless some special treatment or procedure is required that can not be secured at home, they are generally more comfortable, recover more rapidly, and with fewer complications when treated at home than in a hospital. The average elderly patient needs little care, and in many of our hospitals receives less; moreoever, what care he does receive is often not what is most urgently needed. Most of our hospital personnel consists of younger people, and a young nurse in training does not as a rule have the required patience and understanding to make her services satisfactory. Too often these older patients are looked upon as being on their way out of this world, with little to be done for them, meager results, and no reputation to be gained. Thus, when the patient is not able to secure a special nurse, and when no specific treatment is required that can not be given outside of the hospital, the aged patient fares better even in the humblest home than in our modern hospitals. For most elderly patients removal to a hospital is in itself a shock. The change of environment is confusing and many become disoriented and restless and require sedation. In many cases sedation proves harmful by further disturbing the mental equilibrium. Changing from a quiet home to a noisy hospital prevents natural sleep and rest. Changing from home routine to hospital routine nearly always proves detrimental; it not only prevents sleep but destroys appetite and inhibits the normal functioning of digestion and elimination so essential for well-being and recovery. Old people may become frightened and apprehensive. Many do not hear or see well, and this adds to their difficulty in adjusting to hospital life.

At home, from the accustomed low bed, many patients can attain use of the commode or toilet with little assistance. In the high beds of the hospital they at once become helpless. Unless special care is provided, they soon soil the linen,

and decubitus ulcers may develop. If treated by in-dwelling catheters, the result is often cystitis, ascending infectious nephritis, uremia, and death. When the floor nurse is not able to answer their urgent calls, they frequently attempt to climb over the cribsides and injure themselves. If placed in restraint, they act like any animal that is bound and become frightened and lose all self control. Then they are given sedatives, which further decreases the remaining mental powers. Experience with a large number of cases has shown that many old people who were considered in the hospital to be uncontrollable, entirely disoriented and apparently doomed to die, regained their former mental capacity within a short time when brought home, and required neither restraint nor sedation.

The tendency toward smaller living quarters and the scarcity of domestic help is making it more difficult to care for the sick at home, but with the physician's co-operation and proper information many patients can be successfully treated there.

Our younger generation has often been accused of non-cooperation in home care, and tending to push out the old folks to prevent interference with their own activities. In many instances it is not the selfishness of the young people that sends father or mother to the hospital, but the false impression that the parent can and will receive better care and that thereby their recovery will be hastened. In most cases this impression has been created and fostered by the physician, and they are following his lead.

We are all aware that it requires less effort and time on the part of the physician to treat a patient in a hospital than in the average home, and that many younger practitioners, who have been trained in hospital practice alone, find it difficult and distasteful to put the required time and effort into treating the patient at home. Nevertheless, if we as physicians recognize it as a privilege and a duty to relieve suffering wherever it is found, and to use our skill not only in prolonging life but in making it more livable, a consideration of the suggestions we have made will prove rewarding. In giving attention to the personal feelings and comfort of those who have contributed their part to bring about the advantages and comforts that we enjoy, but who are now feeble and dependent on our good will and forbearance, we are permitted in a measure to pay the debt we owe to the past and to receive the gratitude, generally unexpressed, of many of our "have beens."

The medical profession has been credited with extending human life, that is, adding years to its span. If, however, it is unwilling or unable to add comfort and life to those extended years, the value of its service to humanity and to society becomes questionable.

CONCLUSIONS

The aged patient should never be hospitalized if there is any possibility of caring for him at home, unless there is a definite indication for a procedure that can not be successfully carried out at home; even then, hospitalization should be undertaken for only a minimum period. Adherence to this principle will assure a grateful patient, extend his life, make his last days more livable, and in a measure relieve the congestion in our hospitals.

THE PROBLEM OF MALNUTRITION IN THE ELDERLY

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From time immemorial it has been suspected that obesity, undernutrition and dietary imbalance have detrimental effects. All experiments confirm the fact that good nutrition and health are inseparable and that a complete dietary is required for optimal body function. To a lesser extent, it has been recognized also that the well-fed individual is less susceptible to many types of illnesses. Hence proper nutrition is not only important in preventing weight disturbances and specific deficiency states, but perhaps plays an even more vital role in the maintenance of normal health.

Recently the author made a study of 138 patients admitted to the Cuyahoga County Nursing Home with undernutrition and long-term disability (1). Inasmuch as so great a proportion of these patients were in the 60–64 year age bracket and the immediately adjacent 55–59 and 65–69 year brackets, some of the data may have a bearing on the nutrition of the elderly in general.

When the caloric intake is inadequate for the body's energy requirements, loss of weight occurs from endogenous "cannibalization" of the tissues. Therefore, a reduction in body weight from the normal level, when taken together with other evidence of tissue wasting, is *per se* a measure of caloric deficiency. The fat depots are strikingly depleted in victims of undernutrition; thus, in the absence of edema, a loss of body weight is usually a reflection of loss in body fat.

Evaluation of the caloric intake should be the starting point in the search for the cause of malnutrition. The patient should write down for a period of one week the food and beverages consumed at breakfast, lunch, dinner, and between meals. Such a list not only reveals his eating habits and dietary pattern, but also is frequently instrumental in the discovery of food antipathies and idiosyncracies. The general medical history may bring to light additional symptoms of malnutrition, and indicate some etiologic basis.

Because alteration in body weight is still the best indication of a person's diet as it pertains to his current metabolic balance, all elderly and all sick persons should be weighed regularly. The results can be checked against the "ideal weight tables" prepared by the Metropolitan Life Insurance Company, which list the weights for individuals "as ordinarily dressed, with shoes" for each inch of height, taking into consideration at the same time "body build." These tables are reasonably accurate as a guide to the nutritional status.

SIGNS AND SYMPTOMS OF MALNUTRITION

General appearance

In our previous study (1) it was pointed out that physicians are at a loss for words to describe undernourished patients adequately. Some of the terms used

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most frequently are as follows: "poorly or very poorly nourished"; "emaciated wasted or cachectic"; "thin, extremely thin"; "shows evidence of recent or chronic weight loss"; "chronically or very chronically ill"; "poorly developed"; "senile." From these phrases one might infer that in many aged persons, whose appearance generally indicates the chronologic age, there is an underlying malnutrition.

Physical characteristics

The body depends upon an adequate food intake for normal functioning of its various organs. When there has been a severely inadequate nutritional intake, especially of animal proteins and calories, for a prolonged period, irreparable damage may occur in many organs. Fatty metamorphosis of the liver is an example. In the previous study (1) the high incidence of hepatomegaly among patients with undernutrition was stressed. The pathologic changes are fatty metamorphosis and incipient fibrosis due to lipotropic deficiency, although these conditions rarely cause death. Upon the administration of a full diet, the liver usually reverts to normal size within ten to twelve weeks, as determined by careful serial measurements, including percussion of liver dullness.

The gastro-intestinal tract is extremely susceptible to nutritional deficiencies. Hence anorexia is a very early symptom of undernutrition and a real handicap in its treatment. Diarrhea is not uncommon in prolonged cases of malnutrition.

Changes in muscle, skin and mucous membranes

Weakness, frequently unsuspected, is an important manifestation of undernutrition. Fatigue of surreptitious onset may compel persons to give up their jobs or curtail their activities in other ways. Weakness is more likely to be noticed by other people. Eventually, these malnourished persons tend to fall and injure themselves, and then refuse to get up for meals. Finally, they become bedridden and in some instances too weak even to sit upright. The weakness of undernutrition is usually attributed to the so-called "infirmities of old age." This leads one to ask: Why are not these infirmities observed in the well-nourished elderly individual?

Although undernutrition involves the fat content of the body, there is *muscular atrophy* also. In fact muscular atrophy, particularly in the interossei, the upper and lower extremities and the thoracic musculature, is a prominent finding in such patients. Flabby abdominal muscles and prominent depressions in the supra- and infra-clavicular spaces are well known characteristics. In far-advanced cases, atrophy is generalized and the muscles virtually extinct, leaving only skin and bones. The loss of muscle mass which commonly occurs in advanced age should be viewed *per se* as an indication of diminished nutritional reserve. In addition to the obvious emaciation just described, it is necessary to be on the lookout for subclinical degrees of malnutrition and slight muscular atrophy.

The most frequent alterations of the skin in malnutrition are roughness, dryness, scaliness and, in far-advanced cases, a parchmentlike, leathery quality. As a result of the loss of subcutaneous fat, one finds loose, hanging skin, loss of elas-

ticity, sunken eyeballs and cheeks, and diminished turgor. Small wonder that these changes together with a shiny appearance and atrophy are likewise ascribed to the aging phenomenon. A moderate degree of pallor, which tends to bestow upon the malnourished patient a pasty, somewhat washed-out appearance, may be an indication of poor cutaneous nutrition rather than anemia. The patients with malnutrition in our series had a moderate normochromic anemia with an average red blood cell count of 3.95 million and a hemoglobin value of 11.6 Gm. (71 per cent). Interestingly, the changes in the skin and mucous membranes commonly associated with pellagra and other specific avitaminoses were extremely rare in our cases of malnutrition, even when far-advanced.

The frequency of dental abnormalities, especially edentia, among elderly persons has been pointed out many times. It was underscored in our series of patients with undernutrition; one third of them were toothless, and in a great many more there were only functionless teeth with marked caries. Needless to state, mastication was greatly improved with the use of dentures.

Psychiatric aberrations

Cerebral symptoms varying from simple moodiness and emotional instability to the extremes of true dementia and psychoses are observed regularly among patients with malnutrition. Amnesia, irritability, apprehension, confusion and disorientation are the most common manifestations. These disturbances, together with incoherence, restlessness, noisiness, melancholia and depression, are invariably attributed vaguely to "senility," "cerebral arteriosclerosis," or whatnot, without a thought as to the possible role of malnutrition. How easy it is to pass off these cerebral complications of malnutrition as being simply the *ravages* of old age!

CAUSES OF MALNUTRITION

About ten years ago, it was a popular notion that the aged require more protein and vitamins than the young, an idea which developed consequent to finding a higher incidence of nutritional abnormalities in old people. Undernutrition, with its various manifestations, is not a disease exclusively of the aged, but occurs in the so-called normal population as well. When one studies a group of elderly persons having objective evidence of nutritional deficiency in order to learn why the deficiency occurred, one frequently finds the same causes as in younger individuals. They all have one factor in common and this is an inadequate intake of a sufficient amount and variety of foods. Several special problems are encountered in dealing with the geriatric patients. Most of them have one or more chronic conditions. They frequently have poor teeth, fixed dietary habits, and may be parsimonious. There are numerous persons with suboptimal nutrition among all economic classes.

However, there are certain recognized causes which frequently account for obvious undernutrition in the elderly, stemming from the various physical, social, and economic changes to which these people are subjected. In them, subclinical deficiency is probably even more common than overt malnutrition.

1. *Poor food habits*

Why do people eat as they do? Dietary habits are affected by many factors. To some extent they are determined by the physiologic condition of the body, the response of the taste buds (which up to the age of 12 cover the entire mouth and diminish almost to the vanishing point during the second 40 years of life), and the mental state. The elderly person with nutritional deficiencies may be burdened by outmoded medical ideas, may have a pessimistic outlook toward aging, and may have other prejudices not conducive to optimal food intake. The ease with which food is consumed plays a role in an older person's selection of a diet which is frequently excessive in carbohydrate and insufficient in protein. The avoidance of meat and the ingestion of excessive amounts of easily masticated carbohydrates (mainly baked goods) results in an unbalanced diet. The poor nutritional content of these self-selected diets may initiate a vicious cycle.

That poor selection of food results in widespread malnutrition is indicated by the results of nutritional surveys among industrial workers which reveal that the majority do not select diets which meet the recommended allowances of the National Research Council. As I discovered in a large group of elderly patients in the City of Cleveland Infirmary, food preferences were exercised in such a manner that one third of the group became obese, one third remained normal and another third were malnourished. Dietary studies indicate clearly that most persons eat the food of their choice, which is not necessarily the most beneficial food. The most common underlying cause of malnutrition in the patients of our recent study (1) proved to be poor life-time eating habits which could easily be mistaken for simple anorexia.

It should be stressed that the nutritional problems of the elderly frequently can be traced to childhood food idiosyncracies. This, however, is not sufficient reason to gloss over the nutritional defects. The longer the period over which habits have been indulged in, the more rigidly they become fixed. Habits may last longer than life itself, for they may possibly be transmitted from one generation to the next. The emotional constitution of the child and mother may preclude the establishment of an adequate diet. It appears that the finical eating habits observed in malnourished elderly persons originate in childhood, are propagated in adulthood, and become firmly established in later life. Thus, habits of eating represent a very significant role in nutritional problems and are probably one of the greatest obstacles in the path toward obtaining an optimum diet for the majority of persons.

2. *Psychologic aspects of malnutrition and psychiatric states*

The psychologic defense against the aging process takes two pathways, namely, regression and conservatism. The first, regression, is represented by childish actions and such gastro-intestinal symptoms as belching, nausea, vomiting, anorexia and heartburn. Anxieties or unhappiness, especially if long-continued, may lead to such serious anorexia that the individual becomes a victim of undernutrition. Thus it is obvious that psychologic factors may play an important role in the determination of an adequate diet.

Another factor, especially apt to be present in those with cerebral degenerative changes, is a lack of concern about proper food habits. No one is around to make certain that they eat properly, so that the dietary intake of such persons may become restricted. The unpleasant gastric symptoms may be due to anorexia on the basis of atrophic gastritis, or to a fear of eating as observed in chronic superficial and hypertrophic gastritides. Still, the cause of gastritis is emotional and may stem from a feeling of not being wanted, from resentment against financial dependency on others, or from a feeling of insecurity and loneliness brought about by the death of family and friends.

3. *Anorexia*

It is obvious that a persistent loss of appetite must produce undernutrition eventually. However, appetite is an unsatisfactory guide for the selection of nutrients. It is interesting that the patient's appraisal of his own appetite is frequently erroneous, inasmuch as approximately half of the malnourished persons on whom data were available insisted that their appetites were good. The observations of qualified medical personnel often fail to substantiate these claims. However, some patients are well aware of their poor appetites; others refuse food and drink altogether. Undoubtedly, a great many persons classed as "anoretic" actually belong in Group 1 (poor food habits).

4. *Social status and limited funds*

In my experience, one of the most important factors in the malnutrition of the elderly is solitude. Many of these persons are bachelors who live alone in a hotel room or boarding home; and this situation necessitates cooking their own meals—a chore which they usually prefer to forego. A change in living arrangements from a large home to a small apartment or room may result in inadequate facilities for storage and cooking. These inadequacies can be real obstacles to the person who must cook for and eat by himself.

A second sociologic factor in the development of nutritional deficiencies in the aged is limited economic status. An inadequate income precludes the purchase of a sufficient amount and variety of foods. This applies not only to meats but also to citrus fruits. Insufficient funds and the inability to purchase nourishing proteins, however, does not appear to be a frequent cause of malnutrition in the elderly, since money is apparently available from some source.

5. *Failure to recognize malnutrition*

As in the case of other medical diagnoses, failure to recognize the presence of malnutrition actually permits this significant condition to progress unimpeded.

6. *Iatrogenic malnutrition*

All too often, undernutrition is induced in a patient by poorly conceived therapeutic diets. Diets formulated especially for the treatment of particular signs or symptoms of a disease contain inadequate amounts of individual nutrients even for the normal body and, in addition, are frequently insufficient for the super-

imposed demands of the disease process. The most frequently inadequate nutrient is protein. Commonly, protein requirements are not met in patients with ulcerative colitis and other diarrheal diseases, in peptic ulcer (especially during exacerbations), in kidney diseases associated with massive proteinuria, and in cirrhosis and hepatitis. Ulcer diets, in addition, usually are unduly low in calories and markedly deficient in ascorbic acid.

Many low-cholesterol diets employed today are inadequate in high-quality protein and some vitamins. Moreover, by eliminating nutritionally important foods such as milk, eggs and butter, it is difficult to sustain good nutrition. Our current knowledge does not justify the general use of rigid restriction of cholesterol. Since nutritional depletion is readily preventable but difficult to correct, minute attention should be paid to the composition of all special diets.

7. *Inadequate dentition*

Inadequate dentition, either an insufficiency of teeth or poorly fitting dentures, is an important cause of vitamin deficiency in the elderly. This leads to the avoidance of foods (especially meats) which are difficult to masticate but are an important source of the B-complex vitamins.

TREATMENT OF MALNUTRITION

Competent treatment of malnutrition is dependent upon capacity to diagnose nutritional deficiency. Nutritional therapy calls for complete therapy. Ideally, dietary therapy should begin early in life with the infant, and continue through youth and middle age, for if malnutrition is prolonged over many years, the body may be damaged so that it no longer responds efficiently to nutrients. It is impossible to formulate a standard regimen for nutritional therapy; it must be individualized. There is no substitute for clinical acumen to insure the proper application.

Therapeutic regimens for malnutrition should be extensions and modifications of the normal. The caloric value of the diet should be as high as possible. In general, an attempt should be made to supply all necessary nutrients through the diet. The ratio of carbohydrate and protein is less important than the number of calories which they furnish. When carbohydrates are fed simultaneously with proteins, amino acids are maximally utilized for protein synthesis, not only because there is no need for the protein components of the diet to enter the general metabolic pool to be used as a source of energy, but also because the intermediary products of carbohydrate metabolism serve as the necessary precursors for the formation of nonessential amino acids. The diet for the older person must be high, not in *any* protein, but in *superior* protein. The diet must include all the essential mineral elements, especially iron, copper, cobalt, calcium and phosphorus. The best dietary sources of calcium and phosphorus are whole milk, skim milk, and cheese made by the enzyme or rennet process, e.g., brick cheese or swiss cheese. There are so many unknowns in nutrition and metabolism that the focal aim must be to supply a wholesome diet to insure an adequate supply of all known and unknown factors. If an elderly patient objects to meat because of

dental difficulties, use can be made of the canned meat products prescribed by the pediatrician. There is no special virtue in intravenous alimentation, since an adequate caloric intake cannot possibly be achieved except by the oral route.

In our experience it is fruitless to prescribe a high caloric diet without a sufficiently high fat content. The task of maintaining an adequate caloric intake is made unnecessarily complicated by restricting fats. Foods of high fat content (such as butter, cream, cheese or bacon) have the highest caloric value, as fat yields 9 calories of heat per gram as compared to 4 calories per gram for protein and for carbohydrate. Adequate caloric, protein, vitamin and mineral nutrition is much easier to achieve if some fat is allowed. It is difficult to produce a positive nitrogen balance when calories are insufficient, though increasing the caloric intake above a critical level does not further promote the utilization of an adequate amount of protein. Inasmuch as low-fat diets are necessarily low in calories, it is difficult to attain an adequate caloric intake without exceptional persuasion. Moreover, because of their unappetizing nature, low-fat diets usually fail to overcome anorexia. Unfortunately patients, and even physicians, are prone to incriminate fats when there is digestive discomfort.

In the attempt to restore normal nutrition, attention may become focused on purified crystalline compounds and thus be diverted from the total diet and nutrition of the patient. Several adjuvants were administered in our malnourished patients in an attempt to stimulate appetite. Most of them proved ineffectual and were discontinued after a brief trial. Of all the adjuvants, only 3 (thiamine chloride, methyltestosterone with estrogens, and desiccated thyroid) gave promise of success, and these preparations were employed in only a few instances. In a chronic disease hospital, I found undernutrition to be rampant among the patients, although they had been provided with large doses of brewer's yeast over many months and years. This provided living proof that vitamin supplements, without adequate food intake, are not the answer to malnutrition. It always must be remembered that supplemental vitamin capsules are only a reenforcement for the diet, and not a substitute. It is unfortunate that too many people have the impression that the benefits of nutritional therapy can be brought about by "mass" action, *i.e.*, dumping into the patient the maximum amount of every known nutrient.

The mere presentation of food to the malnourished person does not assure its consumption. As a practical point, it should be emphasized that the physician and nutritionist always must make certain that the nutrients are both received and consumed by the patient for whom they are prescribed. In treating malnutrition in the elderly, one may encounter extreme resistance to food, varying from pure obstinacy to open hostility. Many patients can be persuaded to eat the diet provided sufficient effort to feed them is expended by the attending staff, including the physicians. The conviction that malnutrition is reversible should be sufficient incentive for attacking the problem with vigor. Since chronic undernutrition responds slowly in most cases, extreme patience is required.

The physician has a serious responsibility with respect to the caloric intake of elderly persons. More often than not, this task is performed incompletely if not

shirked altogether. The lack of emphasis on this subject in medical curricula and the poverty of published material dealing with malnutrition are not sufficient excuse for this neglect.

Miraculous changes have taken place in malnourished patients, merely by giving them an abundant diet. The biochemical and morphologic aberrations of malnutrition almost always are reversible. Even when obvious gross anatomic lesions have developed, an abundant nutritious diet may reverse the course and permit a complete anatomic and functional recovery. In our previous study (1), using a high caloric diet, a favorable response was obtained in over half of 138 patients. In most of the patients in whom a favorable response was noted, there was a gain in weight ranging from 3 to 52 pounds (average, 14 pounds). Many reflected improvement in nutrition by a better clinical appearance, others by increased physical activity, and still others by improved appetite, better disposition, increased physical activity, increased vigor and a sense of well-being. Similar improvement was noted with respect to muscular atrophy, cutaneous disturbances, gastro-intestinal complaints, and red blood cell counts. The problem of assessing the benefits of therapeutic nutrition is more complicated in persons without overt physical manifestations. However, even in the absence of an obvious deficiency disease, improved nutrition promotes physical emotional well-being and expedites recovery from various illness and injuries.

Education of the public is necessary in order to increase the percentage of well-nourished individuals in the population and to maintain our nation in maximum productivity. The essential role of nutrition in the prophylaxis and therapy of disease should be indicated clearly. The modern conception of nutrition, applied in prospective mothers, infants, children, adolescents and adults, as well as in the geriatric group, will aid in reducing morbidity and mortality in the future.

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HOST-TUMOR ANTAGONISM. V. THE EFFECT OF IONIZING RADIATIONS (RADIUM AND X-RAY) UPON TUMOR AND HOST*

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During the past two decades great advances have been made in the modalities of radiation for the treatment of cancer. These advances, however, have been merely physical in nature (1). The impression is prevalent that the results obtained in the treatment of patients with cancer have not improved. It may be that we do not need more powerful sources for the production of ionizing radiations, but rather a better knowledge of the physiologic actions of those that we already possess. It seems worthwhile to review some of the old work, as well as some of the recent work on the effect of ionizing radiations on the tumor and on the host bearing the tumor. In our anxiety to destroy the tumor cells by using the maximum safe dose of radiation, we may destroy the patient's immunity responses, so that ultimately the tumor may recur.

ATTEMPTS AT RADIATION IMMUNIZATION

Many of the early authors attempted to immunize the host by differential amounts of radiation applied to the tumor. It would seem that some of the principles discovered would warrant careful study. The early literature on tumor immunity was reviewed by Woglom (2), who believed that the devitalization of cancer cells by x-ray or radium and subsequent injection could not result in immunity against a challenge graft of the same tumor.

In 1910, Contamin (3) noted that he could produce immunity to transplanted tumors in mice by inoculating them first with tumor material treated with x-rays *in vitro*. Wedd, Morson and Russ (4) confirmed and extended these observations. They found that the animals were apparently permanently protected. The immunity was acquired even though the irradiated tumor cells never developed into a tumor. Although the Russ group attempted to quantitate the radiation given to the tissue, they did not have available the sensitive instruments known today. They subjected tissue to twice the amount of radiation that would prevent the development of tumors in normal rats. They found the best protection when the immunizing dose was given six to eight weeks before implantation of the tumor. They also attempted to see if immunity could be produced against an established tumor. (Up to that time no immunizing method had been effective against an established tumor.) Russ and his group tried two methods: 1) inoculating an animal that had an established tumor, with irradiated tumor tissue, and 2) irradiating one of two established tumors. By the first method, clear-cut results

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could not be detected with the rapidly growing Jansen rat sarcoma, but were noted with a slower growing tumor. By the second method, irradiation of one tumor did affect the growth of the other established tumor. The authors also showed that when the radiation dose was excessive, the power to immunize was lost. If the dose of radiation was reduced, immunity developed.

Because of the findings in animals, Russ and his co-workers (5, 6) treated 30 patients having far advanced malignant growths—so advanced that complete removal was not possible. It was recognized that, in man, tumors are spontaneous, whereas this is not necessarily so in animals.

At operation, enough tumor was removed to provide material for injection. The growth was sent to the laboratory, where it was broken up in a sterile mincing machine. It was then exposed to the same amount of x-ray radiation as in the animal experiment.

Russ *et al.* thought that an evidence of immunity would be the failure of a metastatic nodule to be established. Other likely evidence of immunity would be a change in the rate of growth of the tumor; this could be detected by measuring the tumor at intervals. Only when the protection was well established would it be possible for the growth to disappear. They mentioned that variations in the growth of human cancer are common, so that great care must be taken before assuming any favorable variation to be a sign of induced immunity.

Twelve patients were described. Five of them died within a rather short time. Five patients with breast cancer were treated, in whom the tumors were far advanced and had metastasized to the axillae. Some of the patients were young, which made the situation more serious. At the time of publication of the article, the first breast cancer patient who had been treated had survived fourteen months. These patients were in good health, and there was no sign of recurrence. There was no evidence of tumor growth in the implants.

Although the results in these patients could in no wise be considered as spectacular, they contained the germ of a good idea. Russ and his colleagues did not have the instruments for measuring the amount of radiation, so his results could not be duplicated.

Controversy arose when Wood (7) and later Wood and Prigosen (8) showed that administration of tumor cells devitalized by x-rays and radium did not prevent successful inoculation with a vigorous tumor. They criticized the small number of animals used by Russ and his colleagues and also the type of tumors. Wood and Prigosen used energetic neoplasms and found that irradiated tissues neither protected against inoculation with tumor cells nor retarded the growths already present. They expressed their strongest disapproval of the use of this method in man. Finally, Wood (7) pointed to the case of a patient in whom the inoculation of irradiated human material was followed by extensive metastases.

The solution to this interesting controversy came through the work of Anna Goldfeder (9), which was reported in several papers from 1940 to 1946. Briefly, she found that the agent in the cells of mouse sarcoma-180 which produces resistance in mice of the same tumor strain was totally destroyed by irradiation with a dose of 6000 roentgens (r). A similar dose prevented the proliferation

in vitro of the same tumor strain. A radiation dose of 4000 to 5000 r prevented proliferation *in vivo* of irradiated implants of the sarcoma-180. Although no active tumor proliferation could be detected, these mice subsequently became resistant to viable, non-irradiated transplants. A dose of 6,000 r destroyed the proliferating power of the tumor cell as well as the immunizing power, but the smaller dose, even though it prevented a detectable tumor, did not prevent immunization. Goldfeder states that in her experiments the amount of radiation was exactly defined and was entirely reproducible, whereas in the studies of Contamin and of Russ and associates and even in the study of Wood and Prigosen, the radiation dosage was approximated. She also commented on the experiments of Kellock, Chambers and Russ (6) with human subjects whose radiation dosage was twice the amount needed to kill the malignant cell *in vitro*. They thus may have destroyed the viability of the cell and also a great deal of the immunizing power. She stated that possibly the delayed appearance of metastases following regression of an irradiated primary growth, may be due to a temporary immunity from the disintegrated tumor cells. This induced immunity may wear off in time, and the dormant tumor cells proliferate again.

This series of articles seems to indicate quite clearly that large doses of radiation, even though they may favorably affect the local tumor implant, may adversely affect any immune reaction that may be present.

LYMPHOID REACTION

A monumental piece of work was carried out by J. B. Murphy (10) and his group, who used x-ray therapy to deplete the lymphatic system of the host.

There is ample evidence that the lymphoid reaction is connected with cancer resistance in mice and other species. Ribbert (11) noted the association between lymphocytic reaction and areas of retrogression in human cancer, and MacCarty (12) demonstrated the salutary prognostic value of lymphoid reaction in breast cancer. The local lymphoid reaction also affects the transplantability of tumors of rats and chickens.

Experiments to test the importance of the lymphoid reaction in tissue grafting and in resistance to cancer had to wait until methods were developed to vary the amount of lymphoid tissue. Murphy and his colleagues showed that lymphoid tissue could be practically depleted by repeated small doses of x-rays and could be stimulated by single small doses of x-rays, dry heat and unsaturated fatty acids. The type of stimulation produced by the three methods varied according to the time and the extent of the response. Thus Murphy showed that the stimulation induced by x-ray radiation is preceded by a period during which there is evidence of the destructive action of this modality on the lymphoid centers. Stimulation then becomes evident, reaching the maximum by the fourth day. With dry heat, stimulation is also preceded by cell destruction of the lymphoid centers, but this negative period is of shorter duration, and the stimulation phase follows promptly and is in greater amount. The effect of injection of olive oil or unsaturated fatty acids is midway between that of the two other methods. In Murphy's experiments, the olive oil or fatty acids were injected intraperi-

toneally as 1 per cent solutions or emulsions made up with distilled water. An unsaturated soap (sodium oleate) and oleic, linoleic and linolenic acids induced an increase in resistance against cancer transplants.

The greatest proportion of mice immune to cancer transplants occurred among those treated with dry heat (60.3 per cent of 102 animals), and the lowest proportion (42.6 per cent of 157 animals) occurred among the mice treated with x-rays. In the mice treated with olive oil or fatty acids, from 45.2 to 57.6 per cent manifested immunity, depending upon the fat used.

Murphy showed experimentally that the lymphoid elements are important in cancer immunity. By studying the natural progress in a tumor transplant, he found that, in a resistant host, there was local round-cell infiltration about the graft. The local reaction was accompanied by a marked increase in circulating mononuclear cells, and by an increase proliferation of the lymphogenic centers. In a susceptible host that supported a growing tumor, the lymphoid tissue underwent marked degenerative changes. Murphy was able to show that experimentally-produced variation in the amount and activity of lymphoid tissue is correlated with a variation in the resistance of the animal to cancer. He felt that the response of lymphoid tissue to a cancer transplant is a general reaction, even though a high degree of local resistance occurs when sufficient local lymphoid reaction is induced. The latter state was achieved by mixing the tumor cells to be transplanted with defibrinated heterologous blood before inoculation.

Murphy also was able to show that round-cell infiltration occurred about foreign-tissue grafts, and that these cells are the mechanism by which the host resists the heterologous transplant. Chick embryo and adult brain allowed the growth of heteroplastic grafts because they manifested no round-cell reaction. When the chick embryo and adult brain were supplied with lymphoid tissue, they became resistant to heterologous transplantation. This feat was accomplished by grafting along with the heterologous tissue a bit of autologous splenic tissue. With an homologous splenic implant instead of an autologous one, there was no resistance to the implantation of heteroplastic grafts in brain tissue. Further, the adult organism was made non-resistant to heteroplastic grafts by means of destruction of the major part of the lymphoid tissue, and resistance to these grafts could be induced again by regeneration of the lymphoid tissue. Murphy felt that the fact that foreign tissues could grow in the brain, where they have no opportunity to be affected by circulating antibodies if present, was against the existence of such a system of protection against heteroplastic tissue grafts. He believed that the lymphoid cell *per se* was the important factor in heteroplastic grafting. At the present time, the overwhelming opinion is that the heteroplastic graft is destroyed by an immunity mechanism. If the lymphocyte is so important an element in the resistance to cancer, one may well ask why metastases grow so readily in lymph nodes. According to Murphy, this occurs only when the function of the lymph node is exhausted. Under the proper conditions, x-ray radiation can exert a stimulative influence on the lymphoid system.

The number of lymphocytes present in an animal's blood prior to tumor transplantation is not an important factor. The degree of success in the matter of

resistance depends on whether or not the animal can produce more cells. Again, the induced lymphocytosis must be associated with increased function of the lymphogenic tissues to be effective. Increasing the number of lymphocytes by causing the spleen to contract under drug therapy does not increase resistance.

Murphy showed that doses of x-ray therapy sufficient to deplete the lymphoid system, lowered the resistance of mice to tumor transplants. He questioned whether intensive x-ray therapy in man may not interfere with the defensive mechanisms, *e.g.*, tumor immunity. In trying to explain why x-ray therapy of skin cancer is so effective, he pointed out that the dosage of x-ray in these circumstances is applied over too small an area to cause any effect on resistance. He believed that x-ray therapy confers a local immunity to the skin area and makes it an unsuitable soil for tumor growth. This refractory state is only confined to the skin layers, and does not even extend to the underlying connective tissue. Thus, the therapeutic value of x-ray radiation in cancer depends upon the cellular reaction of the normal tissues surrounding the neoplasm. Murphy showed this by an ingenious experiment with spontaneous cancers in mice. Skin cancers disappeared promptly after a mild erythema dose of x-rays, but if, after exposure, the tumor was removed and replanted in the same animal in an untreated area, the neoplasm would grow as if no treatment had been given. Conversely, if a graft was implanted in an area previously treated by x-rays, degenerative changes occurred in the cancer cells, even though they themselves had not been treated.

Ewing also felt that there was no evidence of direct destruction of cancer cells with x-rays or radium, but that the cellular exudate induced by these modalities was the essential factor in the curative process.

Summarizing, Murphy believed that there was no evidence that cancer cells were more susceptible than normal cells to x-ray radiation. X-rays in mild erythema dosage rendered the area resistant to cancer transplants but, if used in large generalized dosage, this treatment definitely lowered the resistance of animals to cancer transplants.

CORTISONE AND METASTASES

Recently, Toolan (13) has been able to grow human tumors in rats that had received x-ray radiation or cortisone—forms of therapy which presumably work through the depletion of lymphatic structures. X-ray radiation and cortisone therefore are alike in inhibiting the immune mechanism concerned with heteroplastic tissue transplants.

Duran-Reynals (14) describes a transplantable methylcholenthrene-induced sarcoma (HAS) which has never been known to produce metastases when injected into normal hosts (C-57 black mice). Under the influence of cortisone, this tumor gave rise to lung metastases in a relatively large number of mice (23 per cent). However, in the cortisone-treated mice there was a simultaneous, although temporary, inhibition of the primary tumor. This effect on the local tumor growth was definite. Concurrent with these phenomena, pronounced inflammatory lesions occurred in the viscera due to generalized infection with saprophytic bacteria present in the tumor. The incidence of this inflammatory disease

diminished considerably when antibiotics were added to the inoculation of tumor cells. The bacteria involved had very low pathogenicity for normal mice. In another experiment, it was shown that the induced lung metastases and inflammatory lesions do not persist in subsequent passage into untreated mice.

It has been known for some time that if an adenocarcinoma be transplanted in an homologous strain of mice, the primary tumor will be inhibited and metastases will develop when the mice are treated with cortisone. The effect persists only in treated animals, so that a metastatic lesion transplanted into an untreated animal would result only in an ordinary tumor.

Duran-Reynals found that cortisone caused inhibition of the primary growth of a chemically-induced transplantable tumor, but simultaneously caused the development of metastases and the provocation of a generalized infection by latent saprophytic bacteria. He commented that both bacteria and cancer cells can be observed while subject to the same influence, and that apparently they follow the same laws. Murphy had also noted the similarity of behavior of bacterial cells and cancer cells—both dependent upon the lymphocytic reaction.

It is known that cortisone increases the phagocytic power of the macrophages, leading to rapid fixation of circulating bacteria, while concurrently the digestion of bacteria by the macrophages is blocked, leading to unrestricted multiplication of the bacteria. According to Duran-Reynals, the formation of metastases can be likened to the process of septicemia with secondary abscesses. He believes it possible that enhanced phagocytic function results in fixation and multiplication of both blood-borne cancer cells and bacteria, resulting in metastases and abscess formation.

Summarizing, Duran-Reynals likened the production of carcinomatous metastases to the formation of secondary abscesses from septicemia, both presumably being subject to the same rules. Since cortisone appears to be similar in some of its effects to total body irradiation, irradiation in moderate dosage applied to the cancer cite may suppress the primary tumor; however, if used in excessive dosage (comparable to total body irradiation) it may conceivably predispose to the formation of metastases. The effect of total body irradiation on the immune mechanism in experimental animals, as judged by the antibody response to injected antigens has been documented many times.

EFFECT OF WHOLE-BODY IRRADIATION ON IMMUNITY

It was first demonstrated by Hektoen (15) in 1915 that total body irradiation in experimental animals suppresses the usual antibody response to injected antigens. He ascribed this suppression to destruction of bone marrow and lymphatic tissue. This work has been extended by Jacobson (16) and his associates. These investigators exposed rabbits to 800 r of total body irradiation, some spleen-shielded and others not shielded. Twenty-four hours after exposure, each animal received 1 cc. of a suspension of washed sheep red cells. Non-irradiated control animals likewise received the injections. Blood samples were obtained before treatment and at intervals after immunization. In non-irradiated animals, the hemolytic titers reached as high as 1:5120 by the tenth day, whereas in the

irradiated unprotected animals, the titer never exceeded 1:80 over a much longer period. In spleen-shielded or appendix-shielded animals, a higher titer was reached, usually by the twenty-first day. To account for the difference, Jacobson and his associates found a complete disintegration of lymph nodes within the first twenty-four hours after total body irradiation. In the shielded rabbits, lymphocyte regeneration occurred by the fourth day, whereas in unshielded animals it usually started by the twelfth day. Thus a spleen-shielded or appendix-shielded animal can initiate antibody production in these organs, so that by the fourth or fifth day regenerated lymphatic tissue in other parts of the body can take over.

In order to study the effect of whole-body roentgen irradiation on immunity, tetanus toxoid was injected into mice at varying intervals before and after irradiation (17). The degree of immunity was determined by administering 10 M.L.D. of tetanus toxin two weeks after immunization. Paralysis and death of the mouse one week after the injection of toxin was the criterion for lack of development of the immunity response. Control values were obtained for the radiation effect and the potency of the toxin.

It was found that the larger the dose of radiation, the greater the injury to the antibody-forming mechanism. The closer to the time of irradiation that the toxoid injections were given, the greater was the inhibition of immunity response. Whole body irradiation in sufficient dosage seemed to cause a distinct reduction in the number of circulating phagocytes, and to affect adversely the function of the reticuloendothelial system of the host.

CONCLUSION

A review of both old and recent work on the effect of ionizing radiations on the tumor and the host suggests that our conception of proper dosage may have to be revised. Large doses of radiation may have a salutary effect on the local tumor, but a detrimental effect on the resistance of the host.

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SULFISOXAZOLE (GANTRISIN): CONCENTRATION IN PLASMA AND DIFFUSION INTO THE CEREBROSPINAL FLUID*

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Sulfanilamide actually ushered in the era of chemotherapy, and in point of time the sulfonamide group of drugs has had the longest period of therapeutic use in the treatment of bacterial diseases. The record of safety, efficacy and low-cost justifies their continued use despite the availability of numerous antibiotics. Indeed, there would seem to be at present a resurgence of interest in sulfonamides, not only for the treatment of infections but also as agents (the sulfonylureas) of potential usefulness in influencing carbohydrate metabolism. The continued demonstrations of the effectiveness of the sulfonamides and the renewed current interest had led the authors to repeat and extend studies carried out in previous years, for the express purpose of comparing and delineating more clearly some of the properties that constitute therapeutic and pharmacologic advantages of the more widely used sulfonamides. A specific interest has been the rate and extent of diffusion of the sulfonamide drugs into the cerebrospinal fluid. Work is currently in progress comparing sulfadiazine, sulfamethazine, sulfamerazine, sulfapyrazine, sulfamethoxypyridazine and sulfaethylthiadiazole, and the results will be reported elsewhere.

Sulfisoxazole (Gantrisin) and various mixtures of sulfapyrimidines (chiefly sulfadiazine, sulfamerazine and sulfamethazine) are currently the most widely used sulfonamide preparations. Numerous references in the medical literature document the poor diffusion of sulfisoxazole into the cerebrospinal fluid. Nevertheless, the drug has been found effective in the treatment of meningitis (1–3). Thus clinical experience attests to the therapeutic adequacy of sulfisoxazole—a fact that would not have been predicted on the basis of studies in man (4) and animals (5) which showed that there was very little diffusion of sulfisoxazole into the cerebrospinal fluid in the absence of inflammation. In the presence of inflammation of the meninges, the barrier to diffusion of many substances is markedly lessened; hence, therapeutic results are obtained which would not have been anticipated on the basis of studies carried out in normal man. It seems logical to suggest, however, that the agent that diffuses into the cerebrospinal fluid in greatest degree in the absence of inflammation may be expected to be found in greatest amount in the presence of inflammation. Since the authors were unable to find any considerable body of information on the comparative diffusion of sulfisoxazole and a triple sulfapyrimidine mixture into the cerebrospinal fluid of patients without inflammation of the meninges, the following investigation was carried out.

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CONCENTRATION IN PLASMA

In previous publications (6, 7) the authors have indicated their preference for determination of sulfonamide concentrations in plasma rather than in *whole blood*. Plasma values are almost double those usually reported for whole blood, but determinations on plasma would seem to eliminate the variables introduced by diffusion into, or binding by, the erythrocytes. Plasma concentrations are referred to throughout this report.

In an earlier study (7) sulfisoxazole was compared in the *same* patients with a triple sulfapyrimidine mixture (sulfadiazine, sulfamerazine and sulfamethazine in a 1:1:1 ratio). It was found that, in equal dosage, sulfisoxazole gave rise to more prompt and higher plasma concentrations following an initial dose than did the mixture, but that the sustained plasma concentrations were 1.6 times higher following the mixture than following sulfisoxazole. These observations were qualified by the statement that "the design of the investigation carried out, tested the *lowest average* sulfonamide plasma concentrations maintained throughout the waking day but did not test either the *highest* or the *lowest* levels during treatment that were obtained over a period of days." Thus, the foregoing work left some doubt as to whether sulfisoxazole might not have compared more favorably with the mixture if a different sampling schedule had been followed.

In recognition of this possible shortcoming, a further comparison of sulfisoxazole and the same sulfapyrimidine mixture was carried out prior to the study directed towards comparing rates of cerebrospinal diffusion. From the data presented in our prior publication (7) and from other published information, it seemed that in samples of blood drawn three hours following a dose of sulfisoxazole the concentration of the circulating drug would be at its peak. This time was arrived at by extrapolation from the ascending and descending limbs of dose-response curves following single oral doses of sulfisoxazole.

Five healthy volunteers serving as their own controls were studied in a "cross-over" pattern. *Each* patient received *each* medication according to the same schedule of dosage—4 grams initially at 7 a.m. and 1 gram thereafter at 1, 5 and 9 p.m. on the first day; then 1 gram at 7 a.m. and at 1, 5 and 9 p.m. on days 2, 3, 4 and 5. Following the initial 4-gram dose, blood samples were drawn into heparinized syringes at thirty minutes, and two, four and six hours. On subsequent days samples were drawn immediately prior to the administration of the 1-gram dose at 7 a.m. (actually this sample reflects the ten-hour concentration following the previous 9 p.m. dose) and thereafter at three and five hours respectively. All heparinized blood samples were promptly centrifuged, and the plasma collected and frozen at −4°C. until assay.

The results in detail are presented in Tables 1 and 2, and the average values for free and total drug are charted in Figure 1. The observations following the initial 4-gram doses of the two drugs are in substantial agreement with those previously reported following similar doses (7). Although the dose-response curves were based on more representative sampling, the previous conclusion that plasma concentrations are sustained at a higher level following the sulfa-

TABLE 1

Concentrations of Sulfisoxazole (Free and Total) in Plasma*

Pt.	Sulfisoxazole	Day 1					Day 2			Day 3			Day 4			Day 5		
		Hour					Hour			Hour			Hour			Hour		
		0	½	2	4	6	0	3	5	0	3	5	0	3	5	0	3	5
RB	Free	0	1.04	8.00	14.08	14.32	3.60	7.20	7.76	5.76	7.44	8.40	6.56	9.84	9.12	8.80	9.84	9.04
	Tot.	0	1.44	7.58	13.73	15.17	6.14	9.70	10.56	9.41	10.37	11.81	9.98	13.25	13.06	12.29	13.73	12.48
CC	Free	0	0.00	2.40	15.84	19.20	5.92	10.88	10.40	7.44	9.44	10.24	7.04	9.44	10.88	7.60	10.64	10.40
	Tot.	0	0.00	2.69	15.55	20.35	10.85	13.82	14.59	12.48	13.82	15.26	11.62	13.44	15.55	12.86	15.26	14.40
WN	Free	0	3.44	18.40	17.52	15.20	9.28	12.24	9.84	5.84	6.00	6.40	4.88	8.08	7.60	9.04	11.44	10.24
	Tot.	0	3.17	18.05	19.20	18.24	18.62	22.18	21.02	15.72	16.03	16.42	14.30	16.13	17.38	20.35	21.50	20.64
WP	Free	0	0.00	19.28	21.36	17.92	9.84	13.60	10.24	3.84	9.76	8.00	3.60	9.52	8.48	13.60	8.72	11.04
	Tot.	0	0.00	20.26	24.96	21.81	15.36	19.58	16.03	9.58	14.11	11.81	6.72	12.86	12.86	14.59	19.58	16.03
KO	Free	0	1.36	9.20	23.84	17.52	10.72	12.72	10.24	4.08	6.16	7.20	4.64	6.16	8.00	9.04	12.88	10.40
	Tot.	0	1.25	7.58	24.77	19.97	14.69	15.72	14.21	9.39	8.45	9.79	7.10	8.16	11.23	13.06	16.03	14.30
Avge.	Free	0	1.17	11.45	18.93	16.83	7.87	11.33	9.69	5.79	7.76	8.04	5.34	8.61	8.81	9.61	10.70	10.22
	Tot.	0	1.17	11.63	19.64	19.11	13.13	16.20	15.28	11.31	12.55	13.01	9.94	12.77	14.01	14.63	17.22	15.57

* Dosage schedule: Day 1—4 Gm. initially and 1 Gm. every 4 hrs. for 3 doses. Days 2, 3, 4 and 5—1 Gm. at 7 a.m., and at 1, 5 and 9 p.m. (Hoffmann La Roche lot no. 823–508195).

TABLE 2

Concentrations of Triple Sulfonamide Mixture (1:1:1)† (Free and Total) in Plasma*

Pt.	Sulfisoxazole	Day 1					Day 2			Day 3			Day 4			Day 5		
		Hour					Hour			Hour			Hour			Hour		
		0	½	2	4	6	0	3	5	0	3	5	0	3	5	0	3	5
RB	Free	0	0.80	4.32	16.88	16.72	16.56	16.00	13.20	11.84	11.36	9.68	9.44	11.04	11.12	16.00	15.60	15.20
	Tot.	0	0.96	4.99	17.86	17.95	18.72	18.05	14.98	12.86	12.38	11.14	10.94	11.71	12.48	18.14	17.28	17.28
CC	Free	0	0.00	0.80	11.84	12.00	15.60	16.00	16.00	13.04	12.80	14.00	11.20	12.80	12.80	16.48	16.56	16.48
	Tot.	0	0.00	0.96	12.48	12.67	18.24	15.55	18.72	18.24	14.59	15.72	12.86	14.40	15.36	18.62	19.10	19.20
WN	Free	0	0.64	10.40	5.12	11.12	12.16	11.84	11.84	10.96	11.76	13.60	11.20	12.96	12.48	11.92	11.84	10.96
	Tot.	0	0.96	15.36	6.91	17.86	22.46	21.50	21.31	19.83	20.93	24.10	21.41	23.14	23.14	18.72	20.93	19.78
WP	Free	0	0.00	2.96	18.40	17.92	18.32	20.48	18.32	19.04	20.48	18.88	17.84	18.88	20.48	18.88	17.92	19.52
	Tot.	0	0.00	3.17	20.26	19.39	20.26	23.14	20.26	21.50	21.60	19.83	19.87	20.06	22.56	20.74	19.78	21.50
KO	Free	0	0.96	6.16	9.36	12.40	19.28	18.24	19.28	20.72	17.60	19.20	19.28	20.96	21.60	19.44	20.48	20.08
	Tot.	0	1.15	6.72	10.37	13.63	21.98	20.93	21.41	23.14	19.20	21.98	21.31	20.94	25.15	21.41	22.66	21.98
Avge.	Free	0	0.48	4.93	12.32	14.03	16.36	16.51	15.73	15.08	14.80	15.07	13.79	15.33	15.69	16.54	16.48	16.44
	Tot.	0	0.57	6.44	13.65	16.30	20.27	19.83	19.33	21.11	17.74	18.43	17.17	18.05	19.73	19.58	19.95	19.95

* Concentrations are reported in terms of sulfamerazine.

† The dosage schedule: Day 1—4 Gm. initially and 1 Gm. every 4 hrs. for 3 doses. Days 2, 3, 4 and 5—1 Gm. at 7 a.m., and at 1, 5 and 9 p.m. (Lederle lot no. 4025–184).

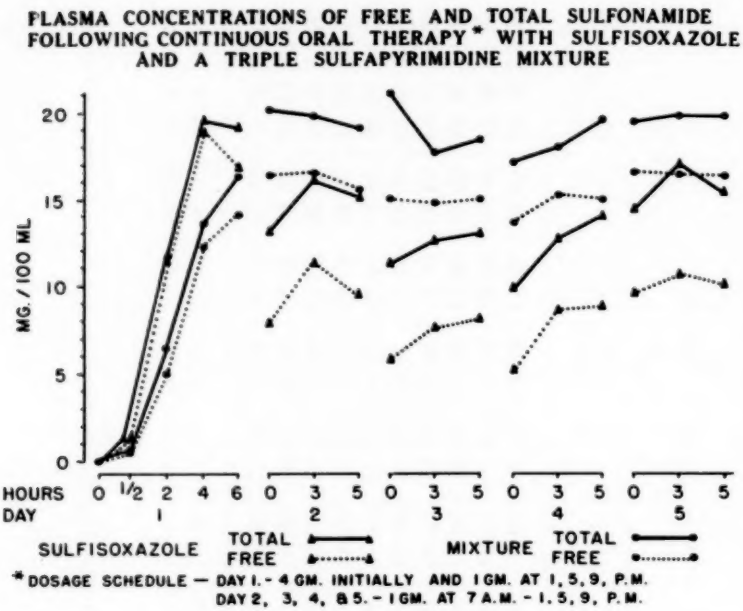
PLASMA CONCENTRATIONS OF FREE AND TOTAL SULFONAMIDE FOLLOWING CONTINUOUS ORAL THERAPY* WITH SULFISOXAZOLE AND A TRIPLE SULFAPYRIMIDINE MIXTURE
MG. / 100 ML
20
15
10
5
0
HOURS 0 1/2 2 4 6 0 3 5 0 3 5 0 3 5 0 3 5
DAY 1 2 3 4 5
SULFISOXAZOLE TOTAL FREE
MIXTURE TOTAL FREE
*DOSAGE SCHEDULE — DAY 1. - 4 GM. INITIALLY AND 1 GM. AT 1, 5, 9, P.M.
DAY 2, 3, 4, & 5. - 1 GM. AT 7 A.M. - 1, 5, 9, P.M.

FIGURE 1

pyrimidine mixture than following sulfisoxazole, was confirmed. In spite of our having chosen for purposes of comparison a daily schedule of dosage which represented only *half* of that usually recommended for sulfisoxazole, the resulting plasma concentrations fulfilled the criteria of therapeutic adequacy as defined for sulfonamide medication (8). The usually recommended daily amount of sulfisoxazole is 8 grams, administered in divided dosage. This would be expected to yield plasma concentrations of the same magnitude as those following the administration of the triple sulfapyrimidine mixture.

DIFFUSION INTO CEREBROSPINAL FLUID

In previous work (9) it was shown that when penicillin was administered in moderate amount by the intramuscular route in water-soluble form there was only slight diffusion into the cerebrospinal fluid of patients with normal meninges. It was further shown (10, 11) that this diffusion of penicillin through the blood-brain barrier was a function of the concentration of penicillin in the plasma. These observations have helped to establish the rationale for banning the intrathecal administration of penicillin for the routine therapy of pyogenic meningitis. When the meninges are inflamed, however, penicillin diffuses across the blood-brain barrier to a much greater degree and concentrations in excess of 1 unit per milliliter are found routinely.

The parallelism between the observations on penicillin and those on sulfisoxazole are striking. It has been shown that the diffusion of sulfisoxazole into the cerebrospinal fluid of normal individuals is inconstant and in small amount—usually 0.25 mg. per 100 ml. or less (4). By the intravenous administration of large amounts of sulfisoxazole, the amount of drug diffusing into the spinal fluid

can be increased to the point that a level approximating 20 per cent of the blood level can be achieved. In the presence of meningitis, concentrations as great as 9.4 mg. per 100 ml. of free sulfisoxazole can be obtained (12). However, even in the presence of meningitis, the diffusion is variable, undoubtedly reflecting the extent to which the integrity of the meninges has been compromised by infection.

Thirty-six patients, predominantly females, were scheduled for routine spinal taps. At two, four and six hours before the tap they were each given a single 4-gram oral dose of sulfisoxazole. Lumbar puncture was performed, and samples of spinal fluid obtained both for routine laboratory study and for estimations of free and total sulfisoxazole. At the same time, samples of blood were drawn from the antecubital vein and prepared for determination of sulfonamide concentration in the plasma. Similarly 41 patients were each given a single 4-gram oral doses of a 1:1:1 triple sulfapyrimidine mixture at two, four and six hours before lumbar puncture, and spinal fluid and blood samples were obtained for sulfonamide estimations.

In Figures 2 and 3 are presented the individual and average *free* sulfonamide concentrations observed in the plasma and cerebrospinal fluid following the administration of equal doses of sulfisoxazole and the triple sulfapyrimidine mixture. The composite average plasma concentrations for this group of patients were of the same order of magnitude as those for normal volunteers (Fig. 1), and for both groups they conformed to previously published data. It is clear that whereas the plasma concentrations following sulfisoxazole were substantially higher than those following the sulfapyrimidine mixture during the period of observation, there was a complete reversal of these concentrations in the cerebrospinal fluid. At two hours the average cerebrospinal fluid concentration of free sulfisoxazole was 0.16 mg. as compared to 0.23 mg. per 100 ml. of the mixed

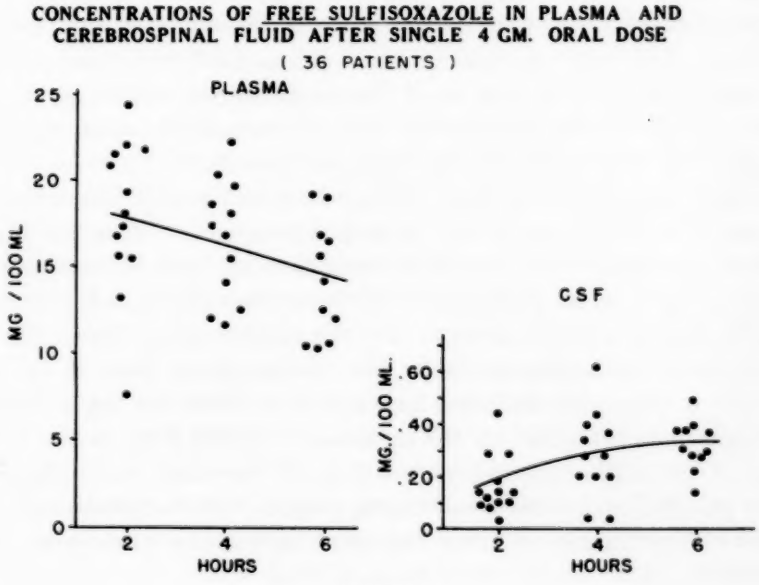

FIGURE 2

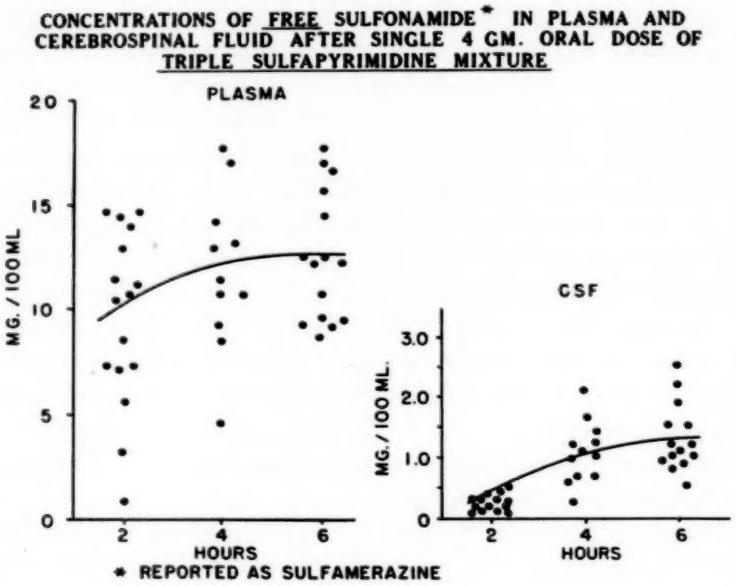

FIGURE 3

sulfapyrimidines. These values represent 1/112 and 1/41 of the plasma concentration of free sulfisoxazole and of the mixed sulfapyrimidines, respectively. At four hours the average spinal fluid concentration of free sulfisoxazole was 0.28 mg. as compared to 0.96 mg. per 100 ml. of mixed sulfapyrimidines, reflecting a ratio of 1/59 for sulfisoxazole and 1/13 for the mixture. At six hours the cerebrospinal fluid concentrations were 0.33 mg. per 100 ml. for sulfisoxazole and 1.28 mg. per 100 ml. for the sulfapyrimidines, or 1/43 and 1/10 respectively, of the plasma concentrations. Although estimations were made of both free and total drug in the cerebrospinal fluid, there was little difference, if any, in the values obtained—a finding to be anticipated, inasmuch as the short period of observation following the initial administration of the drug did not furnish opportunity for significant conjugation of sulfisoxazole or of the components of the triple mixture. Accordingly, only the values for *free* drug are presented.

These observations seem to make it clear that in the first hours following the administration of sulfisoxazole the plasma concentration is much higher than that following the administration of an equal dose of triple sulfonamide mixture. Contrariwise, one or more components of the triple sulfonamide mixture diffuse more rapidly and in greater amount into the cerebrospinal fluid. The fact that the concentration of sulfisoxazole in the cerebrospinal fluid is rising as the concentration in plasma is declining indicates that there is a lag in the reflection of high plasma concentration by the appearance of the drug in the spinal fluid. In the case of the triple sulfonamide mixture, on the other hand, there seems to be a direct parallelism between increasing plasma concentration and increasing spinal fluid concentration. A freer transport across the blood-brain barrier is clearly implied.

DISCUSSION

When the meninges are inflamed they cease to function in normal degree as a barrier to the diffusion of drugs from the blood into the cerebrospinal fluid. Accordingly, drugs such as penicillin, streptomycin and sulfonamides are found in the cerebrospinal fluid in quantity when these drugs are employed for the treatment of meningitis, whereas the same agents are found in very small amounts under normal circumstances. Wider appreciation of these facts has increasingly restricted the intrathecal administration of penicillin and streptomycin in the treatment of meningeal infections. Even though the integrity of the meningeal barrier is breached by infection, there is still an impediment to the free diffusion between blood and cerebrospinal fluid, as shown by the unequal concentration of drug on the two sides of the membrane observed in sulfisoxazole-treated cases (12). Further, there is variability from patient to patient, which unquestionably reflects the differences in severity of the meningeal inflammation. In the presence of meningitis or meningeal irritation, the protein concentration of the cerebrospinal fluid increases—further evidence of the passage of blood components across the blood-brain barrier. Accordingly, not only the free compound is found in the cerebrospinal fluid but also that bound to protein, so that the difference between free and total drug levels as found in the cerebrospinal fluid in the presence of meningitis is much greater than is the case under normal circumstances. The extent to which protein-bound drug is available for therapeutic effect is an open question, but protein binding is almost certainly reversible; hence, the protein-bound drug becomes a potential reservoir that may be effective in treatment.

Certainly the final criterion of worth of any medication is ability to accomplish that for which it is administered. By the practical test of therapeutic trial, sulfisoxazole has been shown to be an effective drug in the treatment of pyogenic meningitis (1–3). This observation stands in opposition to the results which might have been expected on the basis of the poor diffusion of sulfisoxazole through the normal meninges as reported by others (4, 5) and as indicated in this report. It may be asked, therefore, what is the practical importance of the differences between the various sulfonamides, so far as diffusion into the spinal fluid is concerned? This question must remain unanswered until such time as our understanding of the pathophysiology and the most effective treatment of meningitis are more complete than at present. It is entirely possible that the organisms found in the spinal fluid are purely incidental to the primary infection of the nervous system itself, and that if we possessed completely effective antibacterial agents there would need to be no particular concern about the diffusibility of the agent *per se* through the meningeal barrier.

In the presence of meningeal irritation, many poorly diffused drugs pass into the cerebrospinal fluid in significant quantity. Hence, at the time when they appear to be most needed, the drugs may be found in quantity in the spinal fluid. However, it can be postulated that the property of diffusibility into the cerebrospinal fluid in the absence of meningeal irritation might be a positive attribute,

especially if the drug is used routinely in the treatment of infections which potentially may give rise to meningitis. A drug capable of diffusing in significant amount into the cerebrospinal fluid in the absence of meningeal irritation would be expected to prevent the establishment of meningitis. As healing of the meninges occurs, the diffusibility of an agent across the barrier is reduced to the usual low rate; therefore, it may be argued that a drug which can diffuse through the normal barrier may prevent the re-establishment of meningeal infection on the basis of organisms left in the spinal fluid. Such an hypothesis would seem to have more bearing upon infection due to an organism like the tubercle bacillus than upon that due to the pneumococcus or meningococcus. Theoretical though these considerations may be, the primary property of diffusibility across the normal blood-brain barrier would seem to be a desirable characteristic of an antibacterial agent—at least until our understanding of the pathophysiology and treatment of meningitis are better defined. It seems preferable that a therapeutic agent should enter the spinal fluid circulation by natural means rather than by intrathecal injection.

The primary objective of the study reported here was to study the diffusion of sulfisoxazole into the cerebrospinal fluid of normal individuals, and to compare the rate of its diffusion with that of a sulfapyrimidine mixture consisting of equal parts of sulfamerazine, sulfadiazine and sulfamethazine. The data here reported clearly indicate that, when each drug was administered in 4-gram doses, the plasma concentration during the first six hours following administration of sulfisoxazole was much higher than that following administration of a triple sulfonamide mixture. During this same period of observation, diffusion into the cerebrospinal fluid occurred to greater degree with the triple sulfonamide mixture than with sulfisoxazole. At the end of six hours, the concentration of sulfisoxazole in plasma was roughly 40 times greater than in the cerebrospinal fluid; in the case of the triple sulfonamide mixture, the plasma concentration was only 10 times greater than in the cerebrospinal fluid. It seems obvious that one or more components of the sulfapyrimidine mixture diffuse more readily through the normal blood-brain barrier than does sulfisoxazole. The practical importance of these observations is not clear, since sulfisoxazole has been shown to be effective in the treatment of meningitis despite the poor diffusion into the cerebrospinal fluid demonstrated in normal persons.

CONCLUSIONS

The diffusion of sulfisoxazole and of a triple sulfapyrimidine mixture into the cerebrospinal fluid has been studied.

In 36 patients, following the administration of a 4-gram dose of sulfisoxazole, the average concentrations in the cerebrospinal fluid were 0.16, 0.28 and 0.33 mg. per 100 ml. at two, four and six hours respectively. These values represented 1/112, 1/59 and 1/43, respectively, of the concomitant plasma concentrations.

In 41 patients, following the administration of a 4-gram dose of a triple sulfapyrimidine mixture (sulfadiazine, sulfamerazine and sulfamethazine in a

1:1:1 ratio) the average concentrations in the cerebrospinal fluid were 0.23, 0.96 and 1.28 mg. per 100 ml. at two, four and six hours respectively. These figures represented 1/41, 1/13 and 1/10 respectively, of the associated plasma concentrations.

The degree of diffusion of sulfisoxazole observed in this study confirms that in previously reported work. Despite the small degree of diffusion, sulfisoxazole has been shown to be effective in the treatment of meningitis. Thus, it is difficult to assess the practical importance of the foregoing observations at this time.

Acknowledgment

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THE CELL UNIT AND THE AGING PROCESS

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The central concept in medical knowledge has been undergoing a subtle metamorphosis during the past decade. In years past medical knowledge was based upon gross anatomy. During the last century the era of tissue pathology was ushered into being under the aegis of the Vienna school of Virchow and Rokitansky. Thereafter came the decades in which physiology held the limelight. Current emphasis is placed upon histophysiology and histochemistry. This new thought in medical knowledge is reflected in the altered medical curriculum pursued by the most modern American schools of medicine.

Present-day formal medical teaching commences with a complete study of the cell as the center of, and foundation upon which human physiology and pathophysiology begins and terminates. This new educational approach brings into focus the essential value of the cell as the center of biologic functions, as its actions are studied under both normal and pathologic conditions. With the cell unit as the central point, the medical concept is gradually increased as cell is built upon cell to construct tissues, organs, systems, and then the body as a whole.

This reawakening of the basic knowledge to be derived from the cell unit as the site of origin for bodily activity makes it important to examine the cell as the starting point for aging processes.

Although specific scientific evidence is not available, it is not improper to speculate that since the cell unit is the site of origin for growth and disease, it must also be indicted as the site of initiation of the aging process.

Thoughts on this subject, therefore, would abolish the belief that aging is solely the result of a decrease in the functional capacity of the sex hormones as activated by the male and female organs. The decrease in hormonal secretion may be secondary to the altered physical structure and chemical potentiality of the cells composing the endocrine organs involved. The basic cellular alteration with which aging commences and continues may be the deposition of calcium, iron and/or cholesterol-like substances in the cell cytoplasm. Such deposition would alter the normal harmonious physiochemical equilibrium which normally exists between intracellular and extracellular structures. This alteration in physiologic function would affect the permeability of the cell in reference to the proper elimination of the products of anabolism and catabolism.

It is common medical knowledge that atheromatous degeneration and calcific destruction of the aorta are pathologic manifestations of advancing age. The site of the beginning of this change would be in the cell units which collectively form the aorta and large arterial blood vessels. The physiologic disturbance

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producing the pathologic state would be excessive accumulation of calcium in the cell with faulty excretion thereof, and a progressive packing of this element in the cytoplasm. Thus a vicious cycle would be established whereby the more calcium is retained in the cytoplasm, the less is excreted; and the less secreted, the more is retained.

Even as calcium plays the master role in the aging of blood vessels and other structures, so elements of similar physiologic activity may alter the cells in other organs. The sum total of these disturbing influences on cell physiology is the nidus for aging.

SUMMARY

Attention is called to the cell unit as the place where the aging process commences. The disturbance of physiologic function finds its origin in deposition and/or accumulation of certain elements, *e.g.*, calcium, within the cell cytoplasm. The cumulative effect reaches such proportions that purely physiologic processes become pathophysiologic.

THE SOLUTION OF TYPICAL GERIATRIC PROBLEMS IN A RURAL NURSING HOME

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Lake George, N. Y.

The senior author became attending physician to a rural nursing home[1] in the fall of 1956. The following are brief case histories illustrating what relatively simple medical treatment can do in the successful management of geriatric patients.

CASE REPORTS

Case I. A 67-year-old white woman was admitted in August 1956 from a local hospital, with a diagnosis of diabetes and severe eczema with ulceration of both lower extremities.

The hospital provided the diet and insulin schedule which had been previously followed. The authors performed a post-prandial blood sugar screening test of the Wilkerson-Heftmann type and found the blood sugar level to be below 130 mg. per 100 cc. On questioning, it was elicited that the patient used to eat large amounts of candy and other sweets, would often sneak into the kitchen for sugar, and had a very unhappy home life; she preferred to remain in the relative sanctuary of the hospital rather than return home Apparently, also, the leg ulceration was due to self-inflicted wounds.

Insulin was discontinued and the patient was given a regular diet, without untoward sequelae. The ulcerations practically cleared, after her legs were wrapped with zinc oxide bandages to prevent excoriation.

Case II. An 86-year-old white man had been in the nursing home for two years. When first observed by the authors, he was disoriented, irrational, and confused. The nurses reported that these confused states had occurred at frequent intervals in the previous two years. Physical and x-ray examinations revealed a unilateral bronchopneumonia which was secondary to cardiac failure.

The patient was treated successfully with digitalis, penicillin and streptomycin, and has become well-oriented, pleasant, and able to carry on rational conversations.

Case III. A 60-year-old white man, orphaned at the age of 3, had been a county charge since that time. He contracted polio at the age of 5 and had some right-sided motor weakness and contractures of the right arm. He had been in the nursing home for seven years. He had recently fractured a hip, which was treated by pinning. When seen by the authors for the first time, a year after the pinning, the patient was morose, had not moved his injured leg since the operation, and remained bedridden.

He was treated with Ritalin and Thorazine and encouraged to move the hip. At present he asks to get out of bed, sits in a chair, moves the affected extremity, and has consented to learn the use of a wheel chair.

Case IV. An 87-year-old white man had been a patient in the home for seven years. Upon examination, an extensive "rodent ulcer" was observed behind the right ear. According to the patient, the ulcer had been present for fifteen years. Biopsy showed that it was a carcinoma of the basal-cell variety. It proved to be non-radiosensitive, and surgery is being contemplated.

Case V. A 70-year-old white man was admitted in the summer of 1956. At first he was depressed, mentally disturbed, had a severe hacking cough, and suffered from paroxysmal nocturnal dyspnea. An electrocardiogram (portable) was taken, as well as a chest film which disclosed left ventricular hypertrophy and minimal fluid at both bases.

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* Albany Medical College, Class of 1957, on a preceptorship with the senior author.

[1] Lockhart's Nursing Home.

The patient was digitalized and given Thiomeran in a dosage of 1 cc. as needed. Subsequently there was clearing of both mental and physical complaints.

Cases VI–X. Four elderly white men (ages 96, 94, 83 and 75) and one elderly white woman (age 86) had been in the nursing home for between three and six years. When first seen by the authors, they exhibited various forms of psychotic behavior ranging from confusion, disorientation and hallucinations to severe agitation and rages.

These patients are now docile, easily managed, and coherent after institution of treatment with either Thorazine or Frenquil.

Cases XI and XII. Two elderly white men (ages 70 and 75), when first seen by the authors, were "bitter enemies" and engaged in frequent physical altercations. The former was treated with Serpasil and the latter with Thorazine. Marked amelioration of their differences ensued; in fact these men are now quite compatible. The first, a known diabetic taking 25 units of P.Z.I. insulin daily, had been complaining of severe chilliness and precordial pain. He was given 15 units daily of N.P.H. insulin. It was recommended that he have blood sugar screenings so as to regulate his two-hour post-prandial blood sugar level between 130 and 180 mg. per 100 cc., and that his urine be checked daily to see that the sugar level did not exceed 1+ and there was no acetone. To date he has experienced no further episodes of chilliness or precordial pain.

Case XIII. An 84-year-old white man had been a patient for three years. He was a chronic asthmatic with emphysema, suffering from frequent, severe asthmatic attacks which were relieved by intramuscular injection of adrenaline. Physical examination showed the emphysematous chest of a chronic asthmatic, and scattered wheezes but no moist râles. An electrocardiogram indicated mild left ventricular hypertrophy. X-ray examination of the chest was most revealing in that, besides emphysematous changes in the lung and slight cardiac hypertrophy, there was a large fusiform aneurysm of the descending aorta. The order for adrenaline was promptly cancelled and aminophylline (7½ grains very slowly, intravenously) was substituted for treatment of the acute attacks.

COMMENT

The foregoing 13 cases were the most interesting observed by the authors in a rural nursing home currently housing 22 elderly patients, and the therapeutic results were the most satisfying. Symptomatic treatment was carried out by the relatively simple medical means at hand, and these patients were enabled to enjoy a happier and longer life. We believe our methods are applicable to many of the geriatric problems faced by practitioners today, especially in areas not in close proximity to larger medical centers.

PIPRADROL (MERATRAN) IN INSTITUTIONALIZED GERIATRIC PATIENTS*

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Fatigue and depression are commonly observed in the aging individual and in many cases these symptoms have an emotional rather than an organic basis. Older people with very little interest in the present and less hope for the future lack many of the motivations for improvement which exist in younger patients, and their response to therapy is often disappointing.

A series of these patients at the Masonic Home for the Aged has been treated with a new compound, pipradrol (Meratran[1]), in an effort to improve their outlook and behavior. Pipradrol is a new type of central nervous system stimulant (1) which has been reported to be effective in the treatment of depression, without producing adverse effects upon the blood pressure, pulse rate, appetite or sleep (2). No toxic effects have been observed (2).

CLINICAL OBSERVATIONS

Group I

The ages of the first 20 patients chosen for the study ranged from 54 to 96 years (average, 74 years). Ten of the patients were given Meratran (2.0 mg.) at 8:00 a.m. and 12:00 o'clock noon; 10 received a placebo at the same times. At the end of each twenty-five days this order was reversed. The period of observation extended through one hundred days, and changes in activity were recorded as outlined in the Gardner behavior charts (3). All patients were given other medications as needed, and from time to time most of them received salicylates, vitamins, mild cathartics and iron. None was psychotic or showed any signs of mental deterioration.

Five patients dropped out of the study before the first month was over. Two of them complained of nausea and vomiting while taking the placebo; 1 had a severe aggravation of a pre-existent Parkinson's disease; 1 went on a three-month summer vacation; and 1 refused to continue without giving any reason.

Among the remaining 15 patients, Meratran therapy produced definite improvement (increased activity and mental alertness) in 4, noticeable but less marked improvement in 4, and no effect in 7.

Group II

The response to Meratran in the first group was so encouraging that a second group of 10 patients was treated with a combination designated as Alertonic[2] in

* Read by title at the Annual Meeting of the American Geriatrics Society, Chicago, Illinois, May 3 and 4, 1956.

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[1] Meratran is the trade-mark of The Wm. S. Merrell Company, Cincinnati 15, for its brand of pipradrol.

[2] Alertonic is a trade-mark of The Wm. S. Merrell Company for its combination of

a dosage of two teaspoonfuls three times a day, providing a daily equivalent of 2 mg. of Meratran. This material offered the advantage of providing a liquid medication (which many elderly people prefer to tablets) containing Meratran, as well as vitamins, minerals and micronutrients that are frequently deficient in the diets of geriatric patients. The results in each case are summarized as follows:

Patient No. 1 was an 88½-year-old man who complained of weakness and tremor. The pretreatment blood pressure was 140/70 and the pulse was 74. There were no marked abnormalities. The patient was very active but weak during the summer heat. After six weeks of therapy with Alertonic, his appetite improved and he gained 2 pounds in weight. He walked without his cane, his attitude was good, and he slept well. There had been no change in blood pressure.

Patient No. 2 was a 78-year-old man with arteriosclerosis. The pretreatment blood pressure was 120/70. Although confined to bed most of the time, he was mentally active. After taking a total dosage of 2 pints of Alertonic, which he tolerated well, his appetite increased and he gained 4 pounds in weight. He became more active in his home and elsewhere. Blood pressure on his last visit was 126/78.

Patient No. 3 was a 43-year-old man who complained of tiredness. The pretreatment blood pressure was 100/60. After taking Alertonic, he experienced general improvement. His attitude was brighter and he stated that he felt more like working; in fact, he was able to carry on his farm work. He had gained 6 pounds.

Patient No. 4 was a 77-year-old woman with chronic bronchitis, cough, weakness, and depression. The pretreatment blood pressure was 128/78. After a total dosage of 3 pints of Alertonic, her appetite improved and she gained 2 pounds in weight. She felt much stronger and became more active.

Patient No. 5 was a 78-year-old man with low vitality. The pretreatment blood pressure was 160/90. After a total dosage of 2 pints of the combination elixir, he became more active. There was improvement in appetite but no gain in weight. During the hot August of 1955 he did not suffer as much from the heat as he had in past summers.

Patient No. 6 was a 34-year-old man. He was weak, depressed, and exhausted when Alertonic was started. His blood pressure before treatment was 180/60; two weeks after the beginning of treatment, it was 116/68; and four weeks after, it was 122/68. He was able to return to work as a butcher in a super-market, and he has lost no work since the third day of administration of the combination elixir. At the present time he is very active and seems like a new man.

Patient No. 7 was a 52-year-old man who suffered from alcoholic depression, loss of sexual potency and libido, benign hypertrophy of the prostate, and pyuria. After taking the combination elixir, his appetite improved and his desire for alcohol vanished completely by the end of the first six weeks of therapy. His general condition was very satisfactory; he cooperated at home much better and he was no longer depressed.

Patient No. 8 was an 83-year-old female cardiac patient who was suffering from a hip fracture. She was depressed and would not eat. After taking Alertonic for one week, she complained that it burned her stomach terribly. The dose was decreased to one teaspoonful three times a day for the next two weeks. She died of cardiac decompensation.

Patient No. 9 was a 78-year-old, asthmatic woman who had been depressed and complained of poor vitality. The pretreatment blood pressure was 130/70. After six weeks of therapy with the combination elixir in dosage of 2 teaspoonfuls three times daily, her blood pressure was 140/84. After having taken 3 pints of Alertonic she experienced general improvenent; she was more active, her appetite improved, and her attitude became happy and agreeable.

Patient No. 10 was a 64-year-old retired man who complained of weakness, dizziness

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Meratran with vitamins B_1, B_2, B_6, niacinamide, choline, inositol, iodine, calcium, glycerophosphate, cobalt, manganese, zinc and molybdenum.

and depression. He also had mild secondary anemia. The pre-treatment blood pressure was 130/70. After three weeks of treatment with Alertonic he felt stronger and more active, and was no longer quite so sorry for himself. His blood pressure was 124/70. Within six weeks he felt normal. He enjoyed pleasant visits with his family; and his daughter, who was estranged from the family because of her father's depression, returned home to a satisfactory family atmosphere.

Meratran therapy was generally free from effects upon the blood pressure. Mood and attitude improved in the majority of cases, and appetite improved in most. The gain in weight varied from 2 to 6 pounds during the test period. The taste of the drug was apparently satisfactory, since none of the patients refused the liquid medication.

DISCUSSION

There are some old people who are definitely afraid of health and view their disabilities as a sort of accomplishment entitling them to greater prestige, attention and affection. They tacitly resist anything that may threaten to deprive them of the bleak benefits of ill health. Obviously, no drug in itself can have more than a transient value for these patients (4).

It might be well to point out that a person's ability to adjust does not depend alone on the number of years he has lived, but rather on the way he has lived his years. Drugs cannot be expected to supply the answer to deep-seated personality problems, but they can help. Our treatment should have started in youth.

Meratran is potentially more useful when administered in a liquid form containing vitamins and minerals than as the pure drug in tablet form.

CONCLUSION

Results of a 100-day study of 30 aged people living in a modern fraternal home of the Masonic Lodge, State of Oklahoma, and apparently well adjusted in their old age, suggest that pipradrol (Meratran) is of value in the supportive treatment of fatigue states and mental depression. Appetite, sleep, weight and blood pressure were not adversely influenced. In such patients the drug is best given in the form of an elixir containing a metabolic supplement.

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MORTALITY IN ELDERLY PATIENTS AFTER ANESTHESIA AND OPERATION

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As a result of the longer life-span, increased population, and enlarged surgical and anesthetic horizons, operations on aged patients are becoming common. Although, at about the sixth decade of life, certain anatomic and physiologic alterations characteristic of old age are demonstrable in human beings, few operations are too hazardous for the elderly patient who is properly prepared and managed before, during, and after operation. The mortality is only slightly higher than in younger individuals (1–5).

The records of patients 60 years of age and over who had major or minor operations at this hospital for the four-year period 1952–1955 were reviewed. All patients who received a general, spinal or local anesthetic in connection with a surgical procedure, and died either in the operating room or during postoperative hospitalization, were included.

CLINICAL OBSERVATIONS

This series comprises 2,623 patients—1,294 men and 1,329 women. Eighty-five patients (3.2 per cent of the total number) died.

The distribution of patients as to age and sex is shown in Table 1.

TABLE 1

Distribution of Patients According to Age and Sex

Age	Sex		Total	
	Men	Women	Number	Per cent
60–64	194	306	500	19.1
65–69	283	365	648	24.3
70–74	365	350	715	26.9
75–79	268	212	480	19.0
80–89	179	91	270	10.3
90 and over	5	5	10	0.4
Totals	1294	1329	2623	100.0

The mortality for each of the years studied is given in Table 2. Operative mortality did not differ significantly among patients from 60 to 80 years of age, but in the 80–89 year age group there was a marked increase. As only 10 patients over 90 years of age were operated upon, statistical analysis in this group has little value. During 1955 there were fewer surgical patients over 60 years of age; in them, the average mortality was 6.2 per cent.

The causes of deaths are listed in Table 3. Pulmonary diseases caused 40 per cent of the deaths, and cardiac diseases 22.3 per cent. In the 1 purely anesthetic death, cardiac arrest occurred in the operating room but the patient responded to resuscitation procedures. He lived for nineteen days but died of acute renal failure. It was difficult to determine whether or not some of the other deaths

TABLE 2

Mortality after Major and Minor Operations on Elderly Patients at the University of Nebraska Hospital, 1952–55*

Year	Ages 60–64			Ages 65–69			Ages 70–74			Ages 75–79			Ages 80–89			Age 90 and over			Grand Total		
	Total	Deaths	Per Cent	Total	Deaths	Per Cent	Total	Deaths	Per Cent	Total	Deaths	Per Cent	Total	Deaths	Per Cent	Total	Deaths	Per Cent	Total	Deaths	Per Cent
1952	121	2	1.7	176	4	2.4	156	5	3.4	104	3	2.9	75	7	9.1	3	1	33.3	635	22	3.5
1953	125	1	0.8	211	4	2.0	194	3	1.6	133	2	1.6	71	5	7.0	1	0	0.0	735	15	2.1
1954	169	1	0.6	180	3	1.8	223	5	2.2	166	4	2.4	89	7	7.8	4	0	0.0	831	20	2.4
1955	85	6	7.0	81	9	11.1	142	7	5.0	77	2	2.7	35	3	8.6	2	1	50.0	422	28	6.7
Total	500	10	2.0	648	20	3.0	715	20	2.8	480	11	2.3	270	22	8.2	10	2	20.0	2,623	85	3.2

* Including abdominal and thoracic procedures of all kinds (such as operations upon the kidneys, prostatectomies, arthroplasties, and operations for femoral fractures).

TABLE 3

Causes of Death after Major and Minor Operations in Patients over 60 Years of Age

Cause of Death	No. of Patients	Per cent
I. CARDIAC	19	22.3
Coronary thrombosis	[5]	
Myocardial infarction	[5]	
Cardiac decompensation	[9]	
II. PULMONARY	34	40.0
Bronchopneumonia	[16]	
Pulmonary embolism	[11]	
Atelectasis	[4]	
Tension hemothorax or pneumothorax	[3]	
III. OTHER	32	37.7
Carcinomatosis	[4]	
Peritonitis	[2]	
Cerebrovascular accident	[8]	
Hemorrhage	[3]	
Acute renal failure	[3]	
Anesthetic	[1]	
Septicemia	[2]	
Electrolyte imbalance	[4]	
Asphyxia	[1]	
Mesenteric thrombosis	[1]	
Cause unknown	[3]	
Total	85	100.0

TABLE 4

Number of Deaths in Relation to Site of Operation

Site of Operation	No. of Deaths	Per cent
I. THORACIC	6	7.0
Heart and great vessels	[2]	[2.4]
Lungs	[4]	[4.6]
II. INTRA-ABDOMINAL	48	56.5
Exploratory celiotomy	[10]	[11.8]
Gallbladder and common duct	[5]	[5.9]
Stomach	[9]	[10.6]
Bowel*	[18]	[21.2]
Genito-urinary	[6]	[7.0]
III. SUPERFICIAL AND OTHERS†	31	36.5
Total	85	100.0

* Rectosigmoidectomies, colostomies, colectomies and cecostomies.

† Including 12 open reduction and pinning of the hip—about 14.0 per cent mortality.

TABLE 5

Time of Death after Operation and Anesthesia

Interval after Operation	No. of Pts.	Per cent
1. In operating room	0	0.0
2. Within 24 hours	6	7.0
3. Within 3 days	13	13.2
4. Within 1 week	10	11.8
5. Within 2 weeks	28	34.0
6. After 2 weeks	28	34.0
Total	85	100.0

were directly attributable to the anesthetic agent or method. Anesthesia doubtlessly played a contributing role in several cases.

In Table 4 may be seen the number of deaths in relation to the site of operation. About 20 per cent of the deaths occurred in patients undergoing an operation upon the large bowel (rectosigmoidectomy, colectomy, colostomy, or cecostomy). Most were emergency operations performed on subjects in poor physical condition. Twelve patients, most of whom were 80 to 89 years of age, died after open reduction and internal fixation of a fractured hip.

The summary of deaths in relation to the time elapsing from the end of the anesthetic until death, may be seen in Table 5. In most of the elderly patients who died, death occurred two weeks or more after operation.

DISCUSSION

It is not our intention to discuss the deaths in this series in detail. However, it should be noted that the mortality of 3.2 per cent that we found for patients over 60 years of age undergoing operation falls within the range reported by

other investigators. Forastiere (6) from the Bellevue Hospital, New York City, also reported a mortality of 3.2 per cent. Corssen (7) from the University of Texas noted a 5.5 per cent mortality, as did Elman of Barnes Hospital, St. Louis (8). Hingson (9) from Western Reserve University has a low mortality of 2.6 per cent.

SUMMARY

The records of 2,623 patients over 60 years of age who had major and minor operations at the University of Nebraska Hospital in the four-year period 1952–1955 have been reviewed. There were 85 deaths—a mortality of 3.2 per cent. This rate is comparable with those published by other investigators. Pulmonary diseases caused 40 per cent of the deaths. About 20 per cent of the deaths occurred in association with operations upon the large bowel; this mortality rate was high because most of these operations were of an emergency nature, performed on patients in poor physical condition.

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THE SIGNIFICANCE OF THE WOLFF-PARKINSON-WHITE SYNDROME IN GERIATRICS: A REPORT OF 10 CASES

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The Wolff-Parkinson-White syndrome is often called false bundle-branch block, bundle-of-Kent syndrome, or pre-excitation syndrome. It is an anomaly of cardiac conduction which is probably congenital, but apparently may be acquired in a certain percentage of older people. It is not particularly rare, comprising about 5 per cent of cases with wide Q-R-S complexes (1).

Occurring often in healthy people who show no signs of organic heart disease, the presence of the Wolff-Parkinson-White syndrome is frequently revealed by an accidental electrocardiographic finding. Wolff and White (2) collected 52 cases; in 10 (20 per cent) there was diagnosable cardiac disease other than by the electrocardiogram. Though often observed in young people, the syndrome is more often found in the older age group, due to the fact that geriatric patients are subjected to electrocardiographic studies more frequently. People with this cardiac disorder may die in middle or old age, due to superimposed arrhythmias. The autopsy report in a case of Öhnell's (3) is noteworthy. These patients may remain asymptomatic, but are subject to supraventricular tachycardia alternating with normal complexes. Hunter *et al.* (4) state that paroxysmal auricular tachycardia occurs in 5 per cent of cases. In their series, 90 cases were reported from the literature and 10 were added. The superimposed arrhythmia is usually atrial or nodal, less often ventricular; atrial flutter and fibrillation are more rare. Ventricular tachycardia occurs occasionally. Coronary thrombosis may be the terminal event.

Although this syndrome suggests bundle-branch block, there is no block of the bundle of His. The V-lead precordial patterns are not typical of right or left bundle-branch block. It is postulated that conditions which depress the normal pathways may permit functioning of accessory channels such as the bundle of Kent (5, 6), or that the disorder may result from accelerated conduction through normal channels. Prinzmetal and associates (7) have performed animal experiments and have made observations on human subjects which support the theory of accelerated conduction through the atrio-ventricular node.

Early cases of false bundle-branch block were published in the literature by Wilson in 1915 (8), Wedd in 1921 (9), and Bain and Hamilton in 1926 (10). Eleven cases were reported by Wolff, Parkinson and White (11) in 1930; in this article, the disorder was clarified and the practical aspects emphasized.

The Wolff-Parkinson-White syndrome is characterized electrocardiographically by the following findings (12):

1. Short P-R interval of 0.10 second or less.
2. Prolonged Q-R-S interval of 0.11 second or more.

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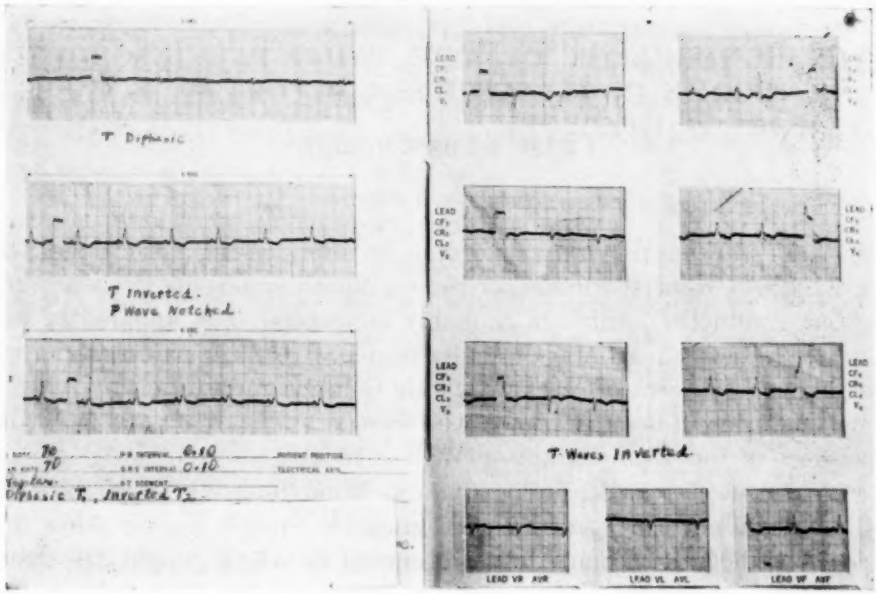

FIG. 1. *Case 1* (*M. W.*). Electrocardiogram, July 18, 1955, denoting variant of Wolff-Parkinson-White syndrome (P-R interval 0.10 sec., Q-R-S interval 0.10 sec.).

3. The sum of the P-R interval and Q-R-S interval equals 0.26 second or less, making the P-J interval normal.
4. There is slurring in the initial deflection of the Q-R-S complex.
5. The P wave is upright.

Slurring is noted in the ascending limb when the main deflection is upward, but on the descending limb when the main deflection is downward. S-T depression, and diphasic or inverted T waves occur frequently.

CASE REPORTS

Ten patients with the Wolff-Parkinson-White syndrome are presented—4 females and 6 males. Their ages ranged from 64 to 84 years. Four patients were in the sixth decade, 3 in the seventh, and 3 in the eighth.

Case 1

M. W. This 81-year-old widow had palpitation, dyspnea and orthopnea since 1941, when she had been digitalized for acute pulmonary edema. She had been maintained on digitalis leaf (0.1 Gm. daily) without symptoms. Earlier electrocardiograms were not available.

Physical examination January 8, 1955 revealed moderate left ventricular cardiac hypertrophy, clear lungs, and blood pressure 170/98. The liver was not enlarged and there was no pedal edema. An electrocardiogram was within normal limits. Auricular and ventricular rates were 70, P-R interval 0.14 second, and Q-R-S interval 0.09 second.

An electrocardiogram July 18, 1955 (Fig. 1) showed marked changes—possible digitalis effect, possible variant of Wolff-Parkinson-White syndrome. Auricular and ventricular rates were 70, P-R interval 0.10 second, and Q-R-S interval 0.10 second. The rhythm was regular, T waves were diphasic and T_2 inverted. The patient had had several bouts of dyspnea.

A tracing July 28, 1955 was unchanged.

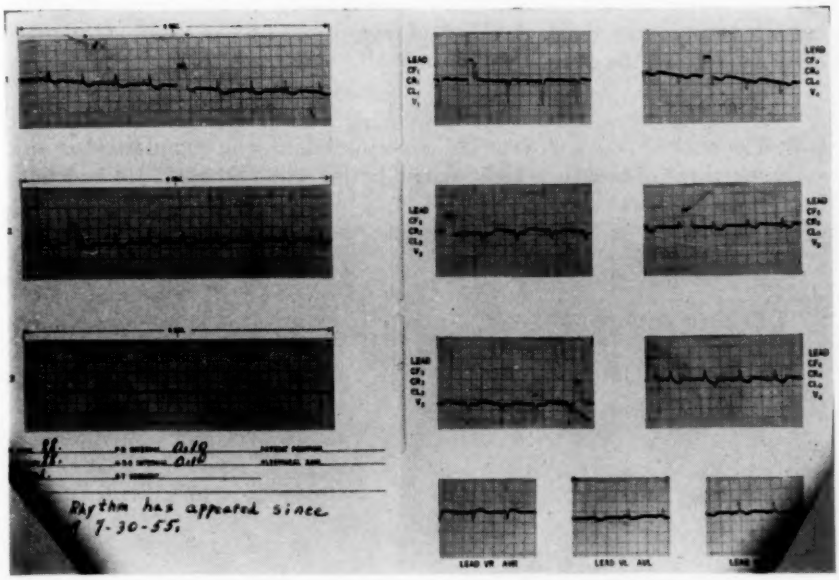

FIG. 2. *Case 1* (*M. W.*). Electrocardiogram, August 5, 1955, showing nodal rhythm (P-R interval 0.10 sec., Q-R-S interval 0.10 sec.).

An electrocardiogram on August 5, 1955 (Fig. 2) showed nodal rhythm. Auricular and ventricular rates were 88, P-R interval 0.10 second, and Q-R-S interval 0.10 second. There had been several episodes of syncope. Digitalis was continued.

Case 2

C. P. The patient was a 79-year-old widow who was first seen on December 18, 1944, with chronic rheumatoid arthritis. Results of a general physical examination and laboratory determinations were otherwise negative. An electrocardiogram was normal. Several electrocardiograms were normal during the next seven years.

On June 14, 1951, a tracing (Fig. 3) indicated typical Wolff-Parkinson-White syndrome, which was asymptomatic until August 4, 1952. At this time auricular flutter developed and persisted for forty-eight hours. Failing to respond to all measures, the patient expired.

Case 3

N. S. This 84-year-old woman had enjoyed good health, but had recurrent bouts of syncope and vague substernal pain. Physical examination revealed a well preserved woman with slight enlargement of the left ventricle, but no cardiac murmurs or arrhythmias. The lungs were clear by auscultation, and this was confirmed in an x-ray film of the chest. Blood pressure was 164 mm. Hg systolic, 94 diastolic. All other physical, laboratory and x-ray findings were normal, except the electrocardiogram (Fig. 4). On November 10, 1950, the auricular and ventricular rates were 70, P-R interval 0.12 second, and Q-R-S interval 0.11 second. The record was interpreted as demonstrating interventricular block.

On December 20, 1950 an electrocardiogram was suggestive of Wolff-Parkinson-White syndrome. Auricular and ventricular rates were 88, P-R interval 0.11 second, and Q-R-S interval 0.12 second. Symptoms of dyspnea and faintness were much improved with quinidine sulfate, 0.1 Gm. three times daily.

On January 2, 1951, the electrocardiographic diagnosis was Wolff-Parkinson-White syndrome (Fig. 5). The Q-R-S complex seemed to vary with the pathway of conduction. The auricular and ventricular rates were 98, P-R interval 0.08 second, and Q-R-S interval 0.13 second. There were a few moist rales in the lung bases, and dyspnea was evident. Upon

digitalization, there was marked relief of symptoms. Subsequent electrocardiograms showed no evidence of the Wolff-Parkinson-White syndrome.

Case 4

W. L. S. The patient was a 69-year-old superintendent who complained of slight cough, fatigue and shortness of breath, which seemed better while at work. He had felt well until

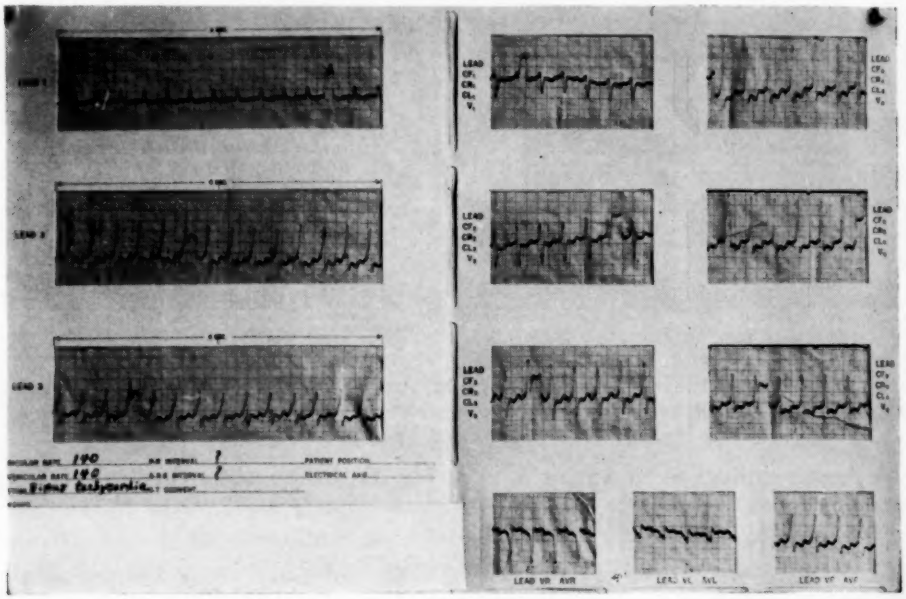

FIG. 3. *Case 2* (*C. P.*). Electrocardiogram, June 14, 1951; Wolff-Parkinson-White syndrome.

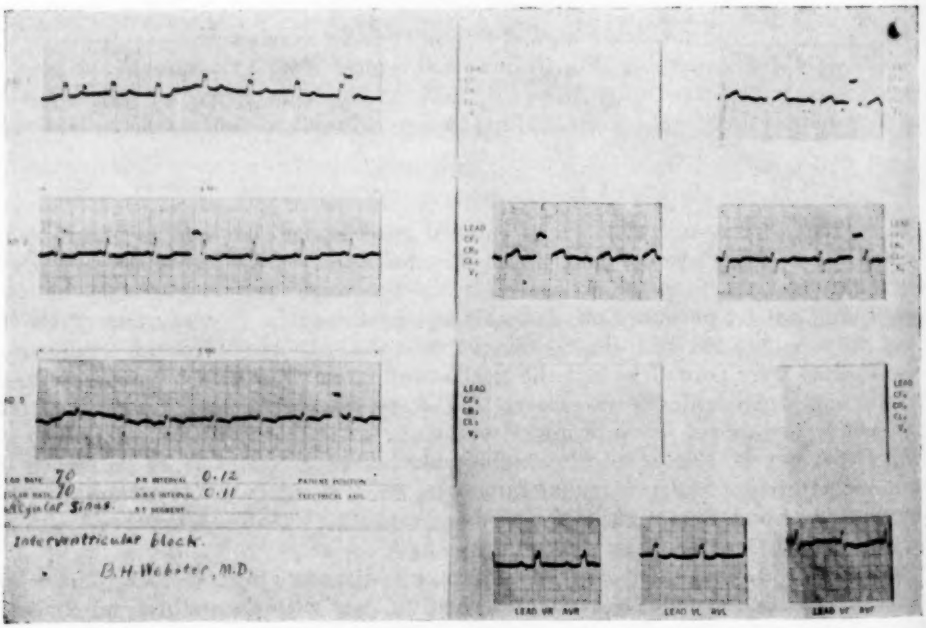

FIG. 4. *Case 3* (*N. S.*). Electrocardiogram, November 10, 1950; interventricular block (P-R interval 0.12 sec., Q-R-S 0.11 sec.).

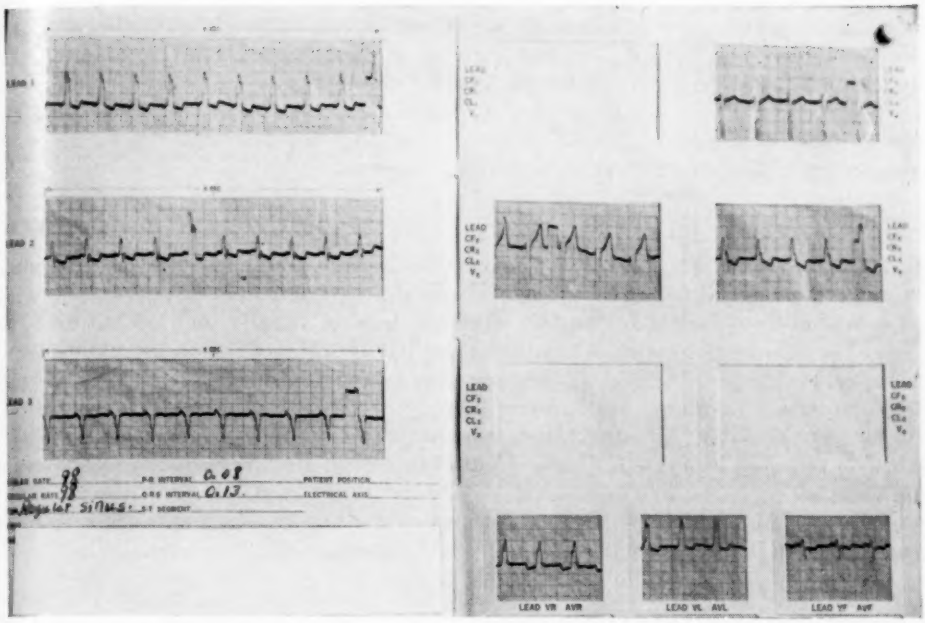

FIG. 5. *Case 3* (*N. S.*). Electrocardiogram, January 2, 1951; Wolff-Parkinson-Whit syndrome (P-R interval 0.08 sec., Q-R-S interval 0.13 sec.).

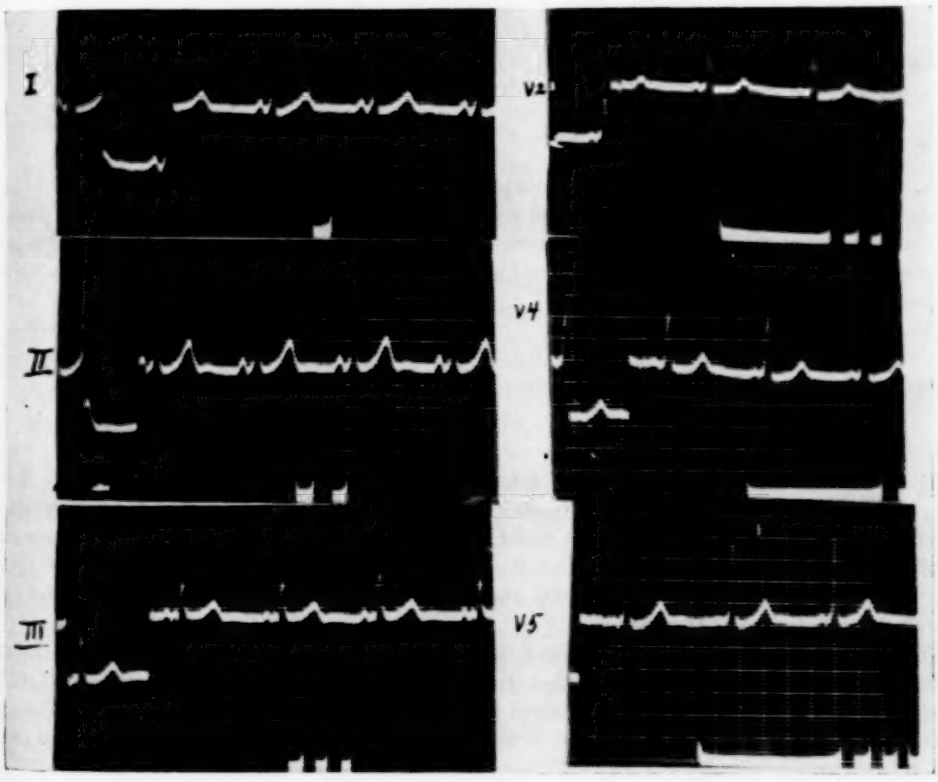

FIG. 6. *Case 6* (*W. G. A.*). Electrocardiogram, April 20, 1948; Wolff-Parkinson-White Syndrome (P-R interval 0.09 sec., Q-R-S interval 0.12 sec.).

three months previously. Physical findings were not remarkable. The heart was not enlarged, the rhythm was regular, and there were no murmurs. Blood pressure was 152 systolic and 90 diastolic. A roentgenogram of the chest showed the heart and lungs to be normal.

Electrocardiograms May 2, 1956, May 14, 1956, June 26, 1956 and September 5, 1956 demonstrated typical Wolff-Parkinson-White syndrome.

Case 5

S. P. This 69-year-old carpenter was first examined March 12, 1956, complaining of exertional dyspnea, fluttering of the heart, and slight cough for the previous year. The heart was slightly enlarged to the left, the sounds were regular, and no murmurs were audible. The blood pressure was 190 systolic and 100 diastolic. The peripheral vessels were tortuous and sclerotic. An electrocardiogram revealed auricular and ventricular rates of 74, P-R interval 0.08, and Q-R-S interval 0.14.

On August 8, 1956 the patient fainted, and an electrocardiogram showed a nodal rhythm which soon reverted to normal. August 15, 1956 the Wolff-Parkinson-White syndrome was again observed.

A sudden severe pain in the chest on September 28, 1956 required hospitalization. Persistent right bundle-branch block was evident in subsequent electrocardiograms.

Case 6

W. G. A. This 72-year-old married farmer was seen April 20, 1948, for a routine physical examination. He was completely asymptomatic, and physical findings were not remarkable. The electrocardiogram (Fig. 6) was typical of that for Wolff-Parkinson-White syndrome, with auricular and ventricular rates of 70, P-R interval 0.09 second, and Q-R-S interval 0.12 second.

Since that time, repeated tracings have been made with the same results. The patient remains asymptomatic. No specific therapy has been instituted.

Case 7

S. F. This 81-year-old woman was examined January 7, 1950, and found to have acute congestive heart failure. The heart was enlarged to left, the rhythm was regular, and no murmurs were audible. The peripheral vessels were sclerotic. Blood pressure was 164 systolic and 98 diastolic. She was digitalized and then given a maintenance dose of digitoxin, 0.1 mg. daily.

An electrocardiogram on January 7, 1950 indicated typical Wolff-Parkinson-White syndrome. Comparison with a tracing July 2, 1952, showed no change. The patient expired suddenly on August 2, 1952, without warning symptoms.

Case 8

H. G. P. This 64-year-old retired merchant had experienced episodes of weakness, dyspnea, palpitation and syncope over a period of five years. Fluoroscopic examination had revealed marked enlargement of the heart, but no murmurs had been audible. Repeated electrocardiograms has been typical for Wolff-Parkinson-White syndrome, with P-R intervals of 0.08 second and Q-R-S intervals above 0.11 second. On several occasions, the syndrome was abolished with quinidine.

On May 1, 1950 auricular fibrillation developed. Upon treatment with quinidine, the rate reverted to normal. Later, intraventricular block developed. Finally, on May 2, 1950, the patient experienced severe substernal pain and shock. An electrocardiogram revealed sinus tachycardia and an acute anterior-wall myocardial infarction. On June 3, 1950 there was superimposed acute pericarditis. The patient expired on that date.

At necropsy, there was evidence of pericarditis. The heart weighed 620 grams. The

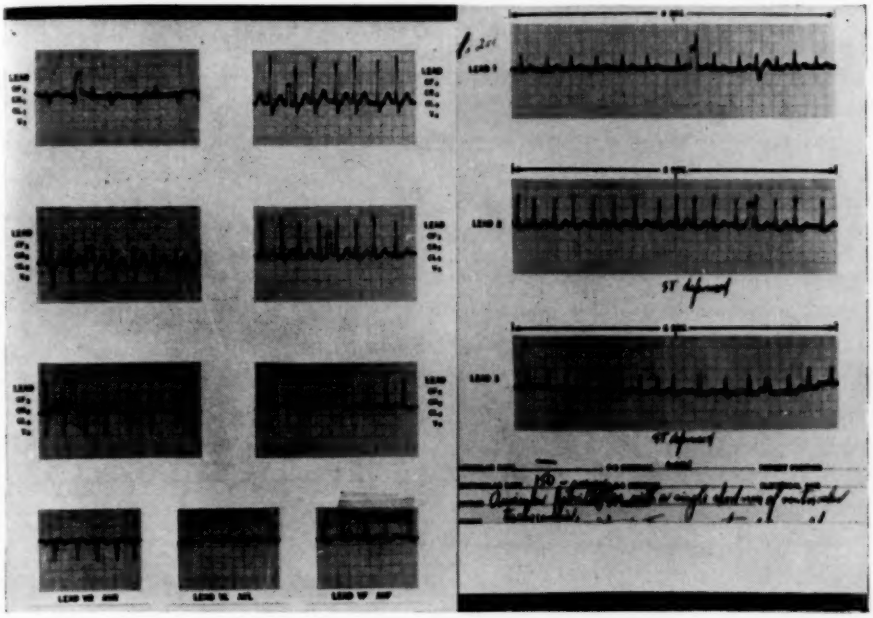

FIG. 7. *Case 9 (H. D.)*. Electrocardiogram, showing auricular fibrillation.

coronary arteries were narrowed, and contained small atheromatous plaques. The myocardium of the left ventricle was thickened. There were small, firm, recent scars in the myocardium of the left ventricle and the interventricular system. The valves appeared normal. Upon careful search, no accessory conduction tissue could be found.

Case 9

H. D. This 68-year-old man had had numerous bouts of substernal oppression for the previous three years. On three occasions, the electrocardiogram demonstrated Wolff-Parkinson-White syndrome, with P-R intervals of 0.09 second and Q-R-S intervals of 0.13 to 0.14 second.

On one occasion, substernal pain was followed by electrocardiographic evidence (Fig. 7) of auricular fibrillation and short runs of ventricular tachycardia. This was soon abolished with quinidine sulfate. Thereafter, the electrocardiogram appeared normal, with regular sinus rhythm, a P-R interval of 0.16, and a Q-R-S interval of 0.08 second.

Eight months later, he was readmitted. The electrocardiogram showed variable auricular and ventricular rates, variable P-R intervals, many premature auricular systoles, and runs of paroxysmal supraventricular tachycardia (Fig. 8). Quinidine sulfate was started, whereupon the electrocardiogram became normal within six hours. The patient is now maintained on quinidine sulfate, 0.2 Gm. three times daily.

Case 10

E. W. The patient was a 78-year-old married salesman who noted occasional exertional dyspnea. Results of physical examination on May 2, 1948 were not remarkable, except for slight left ventricular enlargement. The heart sounds were regular and no arrhythmias were present. An electrocardiogram indicated Wolff-Parkinson-White syndrome, with an auricular rate of 77, a ventricular rate of 77, a P-R interval of 0.08 second, and a Q-R-S interval of 0.11 second.

The patient continued to demonstrate similar electrocardiographic findings, and now at age 86 is well preserved for his age, and without specific symptoms.

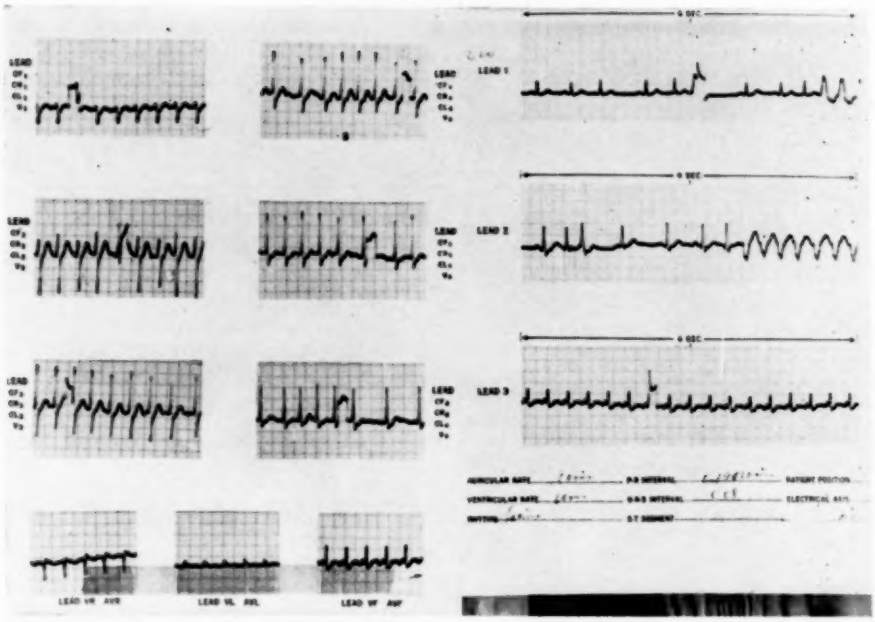

FIG. 8. *Case 9 (H. D.).* Tracing showing variable auricular and ventricular rates, variable P-R interval, and many premature auricular systoles with runs of paroxysmal supraventricular tachycardia.

DISCUSSION

The recognition of the Wolff-Parkinson-White syndrome depends upon the electrocardiographic findings. It is often confused with true bundle-branch block. If there is doubt as to the diagnosis, further tests can be made by applying pressure to the carotid sinus, or by use of the vectorcardiogram. Although this disorder may be functional and apparently unattended by organic heart disease, grave complications, and even death, may ensue.

In our series of geriatric patients with Wolff-Parkinson-White syndrome, 5 patients (Cases 1, 3, 5, 7 and 8) had evident organic heart disease. It is notable that 3 patients (Cases 1, 3 and 5) complained of episodes of syncope which arose from a change in rhythm—nodal rhythm in Cases 1 and 5.

There were 3 deaths in this series. C. P. (Case 2), a 79-year-old woman who was asymptomatic, died of auricular flutter which had persisted for forty-eight hours without response to therapy. S. F. (Case 7), an 81-year-old woman with prior congestive heart failure, expired suddenly without having manifested any other electrocardiographic changes. H. G. P. (Case 8), a 64-year-old man, died of myocardial infarction and pericarditis after a five-year history of Wolff-Parkinson-White syndrome. It is interesting that careful autopsy study in his case did not reveal an accessory bundle of Kent.

The patients in Cases 4, 6 and 10 were practically asymptomatic, and in Case 9 also, except during the episodes of chaotic rhythm.

Many cases of false bundle-branch block revert to normal without therapy. Asymptomatic patients require no treatment. It is generally recommended that

such patients avoid excessive exercise, worry, and excessive use of tobacco, alcohol and coffee. Arrhythmias may be treated with quinidine, procaine amide (Pronestyl), or digitalis. These cases may react poorly to surgery, due to the establishment of ectopic rhythms. Thus precautionary preoperative treatment with quinidine or Pronestyl may be warranted, and digitalization is wise in some cases.

SUMMARY

The Wolff-Parkinson-White syndrome (false bundle-branch block) is reviewed in relationship to geriatrics.

Ten cases are reported in patients ranging in age from 64 to 84 years. There were 3 deaths; 1 was due to myocardial infarction and 1 to auricular flutter, but in the third instance no cause was evident other than the syndrome itself. Three patients experienced attacks of syncope in association with the changes in rhythm.

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Abstracts of Current Literature

LES SIGNES DE LA PANCRÉATITE AIGUË ET LEUR GENÈSE (THE SIGNS OF ACUTE PANCREATITIS AND THEIR ORIGIN).

Bernard, A. *Sem. hôp. Paris* **32:** 2092, 1956; through Ciba Literature Review **1:** 287 (Oct.) 1956.

Acute pancreatitis is often difficult to diagnose because the symptoms usually develop rapidly—within one day or even only a few hours. Moreover, the symptoms are many and varied. This is because of the anatomic position of the pancreas. Once the pancreas has become affected by edema or hemorrhage, it sets up pathologic reflexes in the many organs surrounding it. The clinical picture is dominated by four main symptoms which appear early and are characteristic: 1) violent epigastric pain radiating into the back and caused by irritation of the solar plexus; 2) meteorism (without genuine contraction of the abdominal wall), sometimes accompanied by vomiting. This is due to paralysis of the stomach and intestine, which may sometimes be ulcerated or perforated; 3) elevated blood pressure, provoked by stimulation of the adrenals; and 4) severe dyspnea, the reason for which is that pain restricts movement of the diaphragm. Careful attention to these four principal symptoms should generally ensure a correct diagnosis. Other important signs are pleural effusion (usually on a small scale), pains in the region of the liver (often accompanied by jaundice), albuminuria, hyperglycemia, and a rise in the level of blood and urinary amylase.

GERIATRIC OTOLARYNGOLOGY.

Fabricant, N. D. *Am. J. M. Sc.* **232:** 452 (Oct.) 1956.

This review summarizes some recently published papers on otolaryngologic conditions found in elderly people. Hollender and Lytton (1956) found impaired hearing (the dominant complaint), intensification of vertigo and tinnitus, evidence of nasal and sinus operations in approximately 12 per cent of patients, and chronic rhinosinusitis in 20 per cent (office practice), little nasal allergy, atrophic changes in nasal mucous membranes in 10 to 15 per cent of patients, a weak voice particularly after age 75, chronic hoarseness in about 8 per cent of patients, benign tumors and granulomas of the larynx in 8 per cent, laryngeal carcinoma in 7 per cent, frequent epistaxis probably because of coexistent hypertension, but only infrequent external otitis, in elderly people. Poos (1956) found tinnitus to be common among older persons afflicted with cardiovascular disease, cerebral arteriosclerosis, anemia, and allergic and toxic states. He often found glossodynia, paresthesias, burning tongue, riboflavin-deficiency glossitis, geographic tongue, and atrophic glossitis in older persons. Alexander (1954) pointed out that much can be done to make life more tolerable for deafened persons but that, if the hearing impairment is total or nearly so, little can be done to overcome it. Presbycusis is the most frequent cause of deafness in older persons. Lack of attention on the part of older persons seems to increase apparent hearing defects, and consequently there is difficulty due to confusion of sounds. Pestalozza and Shore (1955) found that in elderly persons discrimination for speech is poor. It becomes poorer as hearing loss becomes greater. Careful enunciation by the speaker, avoidance of confusing noise, speech reading, and the use of a hearing aid will help the person with presbycusis (Simonton, 1955). In the majority of elderly people with vertigo in the study of Droller and Pemberton (1953), the vertigo appeared to be closely associated with arteriosclerosis of the labyrinth. Typical Ménière's syndrome was rarely found. A plateau occurs in tonsillar involution between the ages of 45 and 65 years, and the tonsil generally

does not attain total involution in a lifetime. Tonsillectomy in persons of advanced age is not an exacting procedure and carries no greater risk than in a young person (Keleman, 1954). In younger persons loss of teeth is mostly due to dental decay, but in older persons periodontal disease provides the most important cause for extraction. Aging appears to be more important etiologically in attrition, abrasion, and traumatism than in caries, erosion, and periodontosis (Robinson, 1947). Simple chronic bronchial irritation appears to be the most common cause of chronic cough (Phillips, Phillips and Pecora, 1954). The other papers discussed deal with skin diseases and changes in the blood that may be of interest to the otolaryngologist.

TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE WITH NEOHYDRIN FOR FROM EIGHT TO 65 MONTHS.

Griffith, G. C.; Dimitroff, S. P., and Thorner, M. C. *Ann. Int. Med.* **45:** 7 (July) 1956.

Neohydrin was evaluated in 23 patients, aged 33 to 82 years, who had had chronic congestive heart failure for seven months to eighteen years. More than half of the patients were over the age of 60 years. The entities present were arteriosclerotic heart disease (the most common), inactive rheumatic heart disease, hypertension, and cor pulmonale. The Neohydrin tablets administered for eight to sixty-five months contained the equivalent of 10 mg. of organic mercury in each. The dosage was 1 to 3 tablets daily, with adjustments as necessitated by the patient's clinical status. Some patients were initially treated with the drug parenterally or maintained with it by this route before being changed to oral medication. Other indicated medication, such as digitalis preparations and low-sodium diet, were continued simultaneously. The efficacy of the drug was judged by maintenance of "dry weight" and maintenance of reduction in or absence of rales, peripheral edema, and hepatomegaly. This study confirmed the efficacy of the drug. No clinical evidence of damage to the epithelium of the renal tubules was obtained. The drug, however, is contraindicated in the presence of primary renal disease. Other contraindications are active digestive-tract disease and hemorrhage. Patients with albuminuria and a high blood level of nonprotein nitrogen due to circulatory changes could be adequately and safely treated with the drug for long periods. Patients in the age group above 60 years were able to tolerate the drug without evidence of untoward effects for periods up to five years.

CHRONIC URETHRITIS: A CLINICAL STUDY.

Grimes, W. A.; Cordonnier, J. J., and Humphreys, C. F *J. Urol.* **76:** 83 (July) 1956.

Fifty-one patients with symptoms referable to the lower urinary tract, without pyuria or bacteriuria, and with endoscopic evidence of a normal bladder and an abnormal urethra and/or trigone, were treated for three weeks by one of six treatment plans: 1) dilatation of the urethra with sounds of increasing caliber, followed by instillation of ⅛ per cent silver nitrate twice weekly; 2) insertion into the urethra of a 0.2 per cent Furacin suppository containing also 2 per cent Diperodon hydrochloride, each night for one week and every other night thereafter; 3) the foregoing two methods of treatment in combination; 4) 400,000 units of penicillin (SR) intramuscularly twice weekly, streptomycin 0.5 Gm. intramuscularly twice weekly, and sulfadiazine 1 Gm. four times daily for a week and 0.5 Gm. four times daily thereafter; 5) a combination of methods 2 and 4; and 6) a combination of method 1 with method 4. The majority of patients were 40 to 70 years old. Symptoms had been present for less than three months in a third of the patients, but for more than a year in half of them. The principal symptoms referable to the urethra were frequency of urination, burning associated with urination, nocturia, and urgency. The most frequent extraurethral symptoms were suprapubic pain, pain in the back and hip, dyspareunia, and a feeling of inadequate emptying of the bladder. Twenty-four per cent of the patients had

psychoneurotic or psychotic problems sufficient to warrant psychiatric treatment. This was a significantly increased amount of psychoneurosis and psychosis when compared with that among 51 patients without urethritis who were chosen for comparison. The possible correlation between psychiatric disease and chronic nonbacterial urethritis warrants further study. Some connection between allergic complaints and bladder and urethral symptoms was suggested by the findings among the patients with urethritis. A greater incidence of positive cultures among urethral specimens as compared with urine specimens seemed to indicate infection in the urethral mucosa of the patients with urethritis. The clinical response to treatment was not related to changes in the endoscopic appearance of the urethral mucosa. Patients who were treated by dilatations of the urethra and instillation of dilute silver nitrate, alone or in combination with the antibiotic regimen, responded best. Less benefit was derived from the other treatment regimens. Furacin suppositories proved unsatisfactory and 28 per cent of the patients who started to use them could not tolerate their insertion.

ZUR CORTISONBEHANDLUNG UROLOGISCHER ERKRANKUNGEN (CORTISONE TREATMENT OF UROLOGIC DISEASES).

Hasche-Klünder, R. *Deutsche med. Wchnschr.* **81:** 1088, 1956; through Ciba Literature Review **1:** 254 (Sept.) 1956.

Treatment with cortisone is justified in several urologic conditions. In patients with inflammation of the pubic bone, which generally proves painful, a total dosage of 700 to 1,000 mg. provides rapid and prolonged relief from pain although it has no effect on the pathologic process. Penile induration can be treated by injecting cortisone into the fibrotic plaques. Six injections of 25 mg. given at intervals of one week generally elicit a clear-cut response. Though surgical treatment is indicated in younger patients suffering from stricture of the urethra, in elderly subjects it is advisable to administer cortisone by the oral and intraurethral routes. In ulcer of the bladder, the only improvement noted by the author in response to cortisone was relief from dysuria. Streptomycin encourages shrinkage of the tuberculous bladder—an effect which cortisone (in doses of 25–50 mg. daily) would seem to counteract. In cases of prostatic carcinoma that have failed to respond to removal of the testes or to treatment with estrogen, cortisone may prove beneficial by acting via the pituitary to inhibit the production of adrenal androgens (bloodless adrenalectomy). In addition, cortisone often provides appreciable relief from severe pain, at the same time improving the patient's general status.

CORTISONE ET SECTION D'ADHÉRENCES (CORTISONE AND SECTION OF ADHESIONS).

Huguenin-Dumittan, S., and Medvescek, A. *J. méd. Leysin* **34:** 204, 1956; through Ciba Literature Review **1:** 247 (Sept.) 1956.

When pneumothorax therapy supplemented by thoracocauterization is applied, inflammatory processes characterized by fever and exudation often develop. The authors investigated whether these undesirable reactions could be avoided by the use of antiphlogistic hormones. They compared two groups of patients, each composed of 22 similar cases. In the first group, pneumothorax was performed under antibiotic cover only, whereas in the second, daily doses of 50 mg. of cortisone were administered in addition for ten to fourteen days. This hormone is preferable to corticotropin (ACTH), as it elicits the desired response even in patients with adrenocrotical dysfunction. Moreover, since this hormone treatment lasts for only a short time, there is no risk of inhibiting the activity of the adrenal cortex. Cortisone yielded encouraging results: exudation occurred during the first week among only 10 patients as compared with 15 in the control group. Fever developed in 9, as against 15 of the controls. In all, puncture of the pleural cavity had to be performed only 12 times (9 patients), whereas in the control group 69 punctures (16 patients) were necessary. Even in cases involving division of major adhesions, or of tissue already well organized, only 2

punctures at the most were required. Thus, with the help of cortisone, pneumothorax can be performed with virtually no complications.

DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF EOSINOPENIA IN ACUTE MYOCARDIAL INFARCTION.

Kirkeby, K. *Am. J. M. Sc.* **232:** 50 (July) 1956.

In 149 patients with a diagnosis of myocardial infarction in its early phase, made in the usual manner, eosinophil counts were performed. A count above 50 per cubic millimeter was considered normal. Counts were also performed in 306 patients with conditions usually considered in the differential diagnosis. An early eosinopenia was found in the majority of patients with myocardial infarction. Only 3, 6, and 15 per cent of the counts made on the first, second, and third days, respectively, were normal. The finding of a normal eosinophil count from five to forty-eight hours following an attack thought to be myocardial infarction contraindicates this diagnosis. Eosinopenia is of no value in the differential diagnosis of myocardial infarction from diseases involving severe stress, such as pneumonia, pulmonary embolism, cardiac arrhythmias, acute congestive heart failure, and gallbladder disease. It may, however, aid in distinguishing angina pectoris, as no significant eosinopenia occurred in this disease. A prolonged eosinopenia was found to denote a poor prognosis. This test is recommended in the early phase of myocardial infarction when electrocardiographic tracings may not be conclusive, and when fever and elevated sedimentation rate may be absent. An elevation of the white cell count may be unreliable during this period, so that the eosinophil count probably is a superior indicator.

QUANTITATION OF THE ACTIVITY OF RHEUMATOID ARTHRITIS. 2. RECESSION OF MORNING STIFFNESS AS PATIENTS GO INTO REMISSION.

Lansbury, J. *Am. J. M. Sc.* **232:** 8 (July) 1956.

The duration of morning stiffness, which is present in almost all patients with rheumatoid arthritis, can be accurately judged by the patient. The duration of morning stiffness is roughly correlated with the maximum five-minute fall of erythrocytes in the Cutler sedimentation rate determination, but appears to be unrelated to age, sex, duration of disease and hemoglobin concentration. Thus, in 19 patients in whom the average fall in erythrocytes was greater than the median value of 5.6 mm., the average duration of morning stiffness was four hours, whereas in a group of 22 patients with a sedimentation rate below the median value, the average duration of morning stiffness was 3.2 hours. Three graphic representations indicate that hours of morning stiffness decline according to a regular trend, as a remission of the disease occurs. Morning stiffness is concluded to be a valid index of the general or fibrositic component of rheumatoid activity.

ACUTE CORONARY INSUFFICIENCY: ITS DIFFERENTIAL DIAGNOSIS AND TREATMENT.

Master, A. M.; Jaffe, H. L.; Field, L. E., and Donoso, E. *Ann. Int. Med.* **45:** 561 (Oct.) 1956.

Acute coronary insufficiency represents a sudden transitory inadequacy of the coronary circulation for the requirements of the myocardium. It may occur spontaneously or be induced by factors which increase the work of the heart, decrease the coronary flow, or alter the composition of the blood. Usually a combination of these factors exists. Acute coronary insufficiency is a specific clinical, electrocardiographic and pathologic entity, differing from both angina pectoris and acute coronary occlusion. It indicates a more prolonged and severe myocardial ischemia than does "angina," yet does not present the characteristic electrocardiographic and laboratory features of major infarction secondary to coronary occlusion. There is no change in heart sounds, and no pericardial rub, heart failure, or peripheral embolization. Mild fever, slight leukocytosis, and a slight increase in

sedimentation rate may appear, if significant subendocardial necrosis results. At necropsy, no acute thrombus is present in the coronary arteries. Acute coronary insufficiency is more common than acute coronary occlusion, but may be so mild as to escape recognition. It can develop spontaneously, but often follows severe hemorrhage, tachycardia, marked physical exertion, emotional upset, trauma (surgical or accidental), sudden hypertension, shock, pulmonary embolism and infarction, severe infections, and heart failure. Such cases should be termed "acute coronary insufficiency" secondary to whatever the causative condition may be. Prompt and effective treatment of the precipitating factor may terminate the resultant coronary insufficiency and can even prevent it. In acute hemorrhage, replacement of blood may be life-saving, as are vasopressor drugs in shock and hypotension. The termination of severe tachycardia is also vital. The presence of a precipitating factor in a coronary episode suggests the presence of coronary insufficiency, rather than occlusion. When coronary insufficiency occurs spontaneously, it may clinically resemble coronary occlusion with mild manifestations. The electrocardiographic picture usually serves to distinguish them. Coronary insufficiency may occasionally cause sudden death, but when the patient survives the onset, the prognosis is better than that following occlusion. The treatment of coronary insufficiency and that of coronary occlusion differ; hence, the recognition of the former as an entity is essential. In uncomplicated cases, rest in a chair or merely house confinement has been employed for a period of one to two weeks, avoiding protracted immobilization with the accompanying hazards of peripheral thrombosis commonly seen in older persons. Most patients recover completely and resume work within several weeks. Mural thrombi do not occur; hence, anticoagulants need not be administered. More than two-thirds of the attacks follow a benign course; others are more prolonged and severe and may persist for several weeks or months. An attack of coronary insufficiency may represent the "premonitory phase" of coronary occlusion. Anticoagulant drugs have been recommended in this premonitory or impending phase of acute coronary occlusion but, in the authors' experience, have not prevented the final occlusion. The term "myocardial infarction" used alone is ambiguous and confuses nomenclature and treatment. If employed, it should be modified, so that the terminology is "myocardial infarction secondary to acute coronary insufficiency" or "myocardial infarction secondary to acute coronary occlusion." Acute coronary insufficiency, as defined, is a distinct entity with predisposing and precipitating factors, a definite physiopathologic mechanism, characteristic location of the ischemia or necrosis in the subendocardium, and a more or less characteristic electrocardiogram. Because acute coronary insufficiency can be prevented in the majority of instances, and can usually be cured, its clinical recognition and differential diagnosis from coronary occlusion are essential for definitive treatment. (From authors' conclusions.)

NÄGOT OM SERPASIL OCH DESS ANVÄNDNING INOM PSYKIATRIN (NOTES ON SERPASIL AND ITS USE IN PSYCHIATRY).

Mellgren, A. *Svenska läkartidn.* **53:** 1564, 1956; through Ciba Literature Review **1:** 264 (Sept.) 1956.

Serpasil was employed in a Swedish mental institution to treat 52 patients, almost all of them with serious chronic conditions that had failed to respond adequately to other drugs. Twenty-eight were suffering from schizophrenia, 17 from various types of psychosis, and 4 from paranoia. Initially, Serpasil was administered intramuscularly (1.25 to 2.5 mg. twice daily) for at least one week, after which it was given by mouth in daily doses up to 10 mg. As a rule, one course of treatment lasted forty to sixty days, although in some cases medication was prolonged for several months. Towards the end of the course, the dose of Serpasil should be gradually reduced. Twenty-nine patients responded with marked improvement. The patients became calm and relaxed. Their aggressiveness and anxiety subsided. They were able to sleep better, and their hallucinations were neither so frequent nor so tormenting. The blood pressure declined in every case, especially if the patient was

hypertensive. At the same time, bradycardia and an increase in body weight were often noted. Sometimes extrapyramidal symptoms developed and the patients complained of fatigue and drowsiness. In general, however, the side-effects were insignificant and did not interfere with the course of treatment.

EFFETTO DELLA RESERPINA E DELLA RESERPINA ASSOCIATA A PSICOTONICI IN ALCUNE PSICOPATIE SENILI (EFFECT OF RESERPINE AND OF RESERPINE IN ASSOCIATION WITH TRANQUILIZERS IN SENILE PSYCHOSES).

Negri, R. *Arch. psicol. neurol.* **17:** Suppl. 329, 1956; through Ciba Literature Review **1:** 265 (Sept.) 1956.

This is an account of experience with Serpasil and with Serpasil in combination with Ritalin in the treatment of senile psychoses. Forty patients received Serpasil alone in daily doses of 0.75 to 2.5 mg. for at least thrity days. In 27, more or less marked improvement was noted, especially among patients suffering from excitation, restlessness and emotional disturbances. Forty-nine patients received Serpasil in combination with Ritalin. The average dosage was 0.25 mg. of the former with 10 mg. of the latter, administered several times daily. This largely corresponds to the proportions in which these two drugs are combined in Serpatonil. The patients varied in age from 64 to 91. In some cases, their condition had already deteriorated into complete dementia. In 35 patients, the response was either good or excellent. In general, combined therapy was more effective than Serpasil alone. It not only tranquilized agitated psychotic patients, but effected a "reorganization of the personality" and improved the patients' orientation as to time and space. Initiative again developed in these patients, and they evinced an interest in their surroundings. They were now glad to see relatives whom for months past they had failed to recognize. Particularly striking changes occurred in their behavior. They were able to attend to themselves again, became cleaner in their habits, and took an interest in their personal appearance.

PROSTATIC CORPORA AMYLACEA.

Prather, G. C., and Skinner, D. *J. Urol.* **76:** 107 (July) 1956.

A description is presented of coal-dust or black pepper-like spots in the mucous membrane of the prostatic urethra of the male and the bladder neck of the female. These small bodies are known in the literature as corpora amylacea or concretions, and are identical to similar bodies that may occur throughout the substance of the prostate. On microscopic examination, they consist of periurethral glands or ducts containing plaques, together with amorphous debris and desquamated epithelial cells. Studies by others, and those reported, indicate a nucleoprotein as the substance inside the duct or gland. The nature of the pigment remains obscure. The suburethral concretions may be an incidental finding but their presence has been noted in patients with urinary frequency, urgency, and slight microscopic hematuria, in whom no other abnormality could be found to explain the symptoms. No specific treatment is suggested, although urethral dilatation and irrigation have been helpful in improving symptoms. Resection of the involved area in the female, or prostatectomy in the male, may be considered only if symptoms are severe. (From authors' summary.)

PREDNISONE E PREDNISOLONE, MEDICAZIONE ANTIREATTIVA ELETTIVA DELLA TUBERCOLOSI POLMONARE (PREDNISONE AND PREDNISOLONE, ANTIREACTIVE MEDICATIONS IN PULMONARY TUBERCULOSIS).

Reale, M.; Garaventa, A.; Paoli, G., and Costa, G. *Minerva med.* **47**/1: 1764, 1956; through Ciba Literature Review **1:** 251 (Sept.) 1956.

Thirty patients suffering from various types of tuberculosis were treated with prednisone and prednisolone in the hope that the antireactive effect of these hormones would enhance

the tuberculostatic action of streptomycin and isoniazide. The initial dosage was 30 mg. daily in six fractional doses. This dosage was maintained for ten to twenty days, and then gradually reduced to 10 or 5 mg. daily. Most of the paitnets were given a total dose of 1,000 mg. over a period of forty to sixty days. In less severe cases, the dose was 600 to 700 mg. No special diet was imposed, as the hormones had little or no influence on the water and mineral balances. In 23 patients the results were good or excellent, and in the remaining 7, fair. These hormones exert their full effect during the phase in which pulmonary tuberculosis is developing, their intense antireactive properties helping to promote the healing of specific lesions. In chronic cases, they are of value in inhibiting the tuberculous process. They have a prompt and favorable influence on the fever, appetite, erythrocyte sedimentation rate, and sputum—an influence that is sometimes apparent within only a few hours. Concomitantly with the satisfactory progress revealed in the anatomic and roentgenographic findings, the patient's general condition improves and the toxic symptoms disappear. Both hormones proved equally effective and were equally well tolerated.

HAZARDS IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION.
Russek, H. I. *Am. J. M. Sc.* **232:** 403 (Oct.) 1956.

"Routine" programs for the treatment of a patient with acute myocardial infarction should be discouraged and treatment planned for each person individually. The use of potentially dangerous drugs is unjustified without a clear-cut indication. The risks from drugs and methods of therapy are summarized: *Nitroglycerine* may precipitate or aggravate the shock syndrome, reduce coronary flow, and excite dangerous ectopic tachycardias. *Morphine* may produce abdominal distention, urinary retention, respiratory depression, vomiting and retching. It may also increase the susceptibility to ventricular ectopic rhythms, increase biliary pressure, and exert antidiuretic and hypotensive effects. *Oxygen* may have an adverse psychogenic effect or produce claustrophobia through the use of the tent. The nasal catheter may cause hacking and coughing, and the mask may induce "suffocation" and anxiety. The administration of 100 per cent oxygen can lead to ventricular fibrillation. *Anticoagulants* can cause hemorrhagic complications and even death. During their administration, the physician sometimes acquires a false sense of security. *Hospitalization* carries with it the risk of ventricular fibrillation, cardiac asystole, and shock from psychic and physical factors, especially if the patient is moved during the first forty-eight hours. There may also be an increased tendency toward psychoneurosis and anxiety states. *Bed rest* may be accompanied by the loss of muscular and vascular tone, constipation, anxiety states, and thromboembolic complications. *"Chair treatment"* risks ventricular fibrillation, cardiac asystole, shock or cardiac rupture due to stress, augments the hypotensive effect of opiates, and gives the patient a false sense of well-being. *Digitalis* intoxication can be easily induced. Digitalis has strong vagal effects, one of which may be the production of atrial fibrillation. Its administration is potentially dangerous in the presence of ventricular tachycardia, as it results in ventricular fibrillation. Vomiting, diarrhea and nausea are common with *quinidine* orally. Electrocardiographic control is necessary during its intravenous use in order to prevent cardiac arrest or ventricular fibrillation. *Pronestyl* may cause marked depression of blood pressure, ventricular fibrillation, or cardiac arrest. *Pressor agents* sometimes cause excessive and dangerous elevations in blood pressure and may aggravate congestive heart failure. Levophed can cause local gangrene upon extravasation into the tissues. Rapid intravenous injection of aminophylline may cause so much vasodilatation as to precipitate collapse or even death. Too rapid injection may also cause lesser degrees of peripheral arteriolar dilatation resulting in palpitation, headache, nausea, chest pain and syncope. Intravenously, *papaverine* may produce a sharp drop in blood pressure, precipitate collapse and fatal ventricular fibrillation. *Alcohol* should not be given in acute coronary occulsion, as it may increase the pulse rate, produce ectopic beats, or precipitate paroxysmal tachycardia.

ARLIDIN: A CLINICAL EVALUATION OF A PERIPHERAL VASODILATOR WITH SELECTIVE ACTION ON MUSCLE VESSELS.

Stein, I. D. *Ann. Int. Med.* **45:** 185 (Aug.) 1956.

Arlidin, a peripheral dilator that affects the vascular bed of skeletal muscle, was tested in 191 patients with arteriosclerosis, 21 with recent thrombotic closure, and 8 with thromboangiitis obliterans. In each, intermittent claudication was the cause of disability. Tests were performed to estimate the vascular reserve of each patient before therapy. One 6-mg. Arlidin tablet was administered three times daily for one week. In the absence of a response, the dosage was increased to two tablets three times daily. Appreciable improvement was obtained after two to three weeks of treatment in the patients who responded. Sixty-five to 70 per cent of patients with peripheral arteriosclerosis leading to acute or chronic development of symptoms of muscle ischemia were improved. The 8 patients with thromboangiitis obliterans experienced moderate or marked improvement. The relief or modification of intermittent claudication was not related to obvious physical improvement in the extremities nor to changes in the results of specific tests other than the exercise tolerance tests. There was a significant increase in the ability to walk. In patients with patent femoral arteries, the intra-arterial injection of 6 mg. of the drug brought about an average increase of blood flow in the calf, of 300 to 400 per cent. Arlidin is concluded to be an effective dilator of blood vessels in skeletal muscle, and indicated in the treatment of intermittent claudication.

ERFAHRUNGEN UND GEGENWÄRTIGER STAND DER ALLGEMEINEN CORTISONTHERAPIE IN DER DERMATOLOGIE (EXPERIENCE WITH AND PRESENT STATUS OF CORTISONE THERAPY IN DERMATOLOGY).

Tappeiner, J., and Wodniansky, P. *Klin. Med.* **11:** 271, 1956; through Ciba Literature Review **1:** 283 (Oct.) 1956.

The following indications for cortisone therapy are reviewed: acute and subacute lupus erythematosus, dermatomyositis, some cases of rapidly progressive scleroderma, and dermatitis herpetiformis. Cortisone also yields impressive results in diseases of the pemphigus type, the prognosis of which is otherwise hopeless. With this hormone in initial daily doses of 600 to 800 mg., it is possible in nearly every case to overcome the crisis, to suppress the bullous eruptions within a few days, and to eliminate the severe fever that is often present. As a rule, the treatment lasts several months. Sixteen cases of histologically confirmed pemphigus have been under observation for several years. The fact that none of these patients has died from the disease is in itself a great achievement, but in addition, 6 of them have been symptom-free for about two years, and a further 8 are being maintained on an ambulatory basis with daily dosages of 25 to 200 mg. of cortisone. Some of them suffer occasionally from outbreaks of bullae, but these have little adverse effect on their general condition.

INDICATIONS DU TRAITEMENT PAR LA CORTISONE DANS LES HÉPATITES AIGUËS ET CHRONIQUES (INDICATIONS FOR TREATMENT WITH CORTISONE IN ACUTE AND CHRONIC HEPATITIS).

Vachon, A. *Sem. hôp. Paris* **32:** 2498, 1956; through Ciba Literature Review **1:** 284 (Oct.) 1956.

The primary purpose in administering cortisone or prednisone in cases of hepatitis is to assist the liver in replenishing its stores of glycogen and to stimulate the flow of bile. The antiphlogistic action of these hormones also has a general beneficial influence, although they cannot be expected to have a direct effect on the hepatitis virus. Hormone treatment

brings prompt relief from anorexia and asthenia, as well as reducing quickly the patient's temperature. The symptoms of jaundice, however, are much more slow to respond. In cirrhosis of the liver, hormone therapy, combined with conventional methods of treatment, is particularly indicated in the more severe forms of this disease. The diuretic effect which is brought about by an increase in filtration and a reduction in reabsorption via the renal tubules, results in rapid dispersal of edema and ascites. The advantage of prednisone over cortisone is that it has a more potent diuretic action and causes less water and electrolyte retention. Even so, a low-salt diet is advisable with both these hormones. The recommended daily dosage in the initial stages of treatment is 150 mg. of cortisone or 20 to 30 mg. of prednisone orally, followed by smaller doses. Treatment for hepatitis lasts two to four weeks, but for patients with cirrhosis more prolonged therapy may be required. In serious cases or in patients with hepatic coma, at least 300 to 400 mg. of cortisone must be administered daily by the parenteral route, preferably together with glucose and glutamic acid.

AN ANALYSIS OF 200 ADMISSIONS FOR MASSIVE UPPER GASTROINTESTINAL BLEEDING.

Zimmerman, S. L.; Engel, E. F.; Lapidus, B.; Bradley, E. A., and Claytor, H. *Ann. Int. Med.* **45:** 653 (Oct.) 1956.

An analysis was undertaken of the results of treatment of upper gastrointestinal tract bleeding among 200 patients bleeding from the following causes: duodenal ulcer, 123; prolapse of the antral mucosa, 10; bleeding from undetermined site, 13; gastric ulcer, 22; cirrhosis, 29; and gastric malignancy, 3. The following conclusions were drawn from scrutiny of the cases of bleeding duodenal ulcer: 1) That the over-all mortality rate from bleeding duodenal ulcers (0.8 per cent) compared favorably with the results reported elsewhere. 2) That medical management of the bleeding period is adequate, emergency surgical intervention having been necessary in only 2 cases, or 1.6 per cent. 3) That there is recurrence of bleeding in 37 per cent of cases without surgery, and following elective gastric resection the percentage of further bleeding drops significantly. Gastric ulcer in 22 patients was demonstrated by roentgenographic examination, gastroscopy, or at necropsy. The incidence was highest in the 50–59 year age group. Treatment consisted of sedation, feeding of boiled skimmed milk, antacids in some patients, intravenous fluids, blood replacement by repeated transfusions, and Wangensteen suction in a few instances. Three patients died as a result of the gastric hemorrhage—a mortality rate of 13.6 per cent due to bleeding. This high rate is the basis for the present concept of earlier surgical intervention in patients with bleeding gastric ulcer. None of the 10 patients with bleeding ascribed to prolapsed antral mucosa died. A gastric ulcer in one of them healed under medical management. No deaths from bleeding occurred among patients bleeding from an undetermined site. All 3 patients with carcinoma of the stomach died from hemorrhage. The mortality rate among cirrhotic patients with hemorrhage was 27.6 per cent, 3.4 per cent being due to hemorrhage and the remainder to liver failure precipitated by hemorrhage. The control of bleeding contributed little to the length of survival. Medical management consisted of: 1) Absolute bed rest and quiet. 2) Sedation with drugs other than morphine; a progressive ulcer regimen; one-hourly or two-hourly feedings; antacid when food was not continued through the night; blood transfusions; careful attention to hematocrit, blood pressure, electrolyte balance and urinary output; and the avoidance of overloading the circulation, especially in the elderly arteriosclerotic patient. 3) Control of bleeding due to esophageal and gastric varices associated with portal hypertension, through the use of the Blakemore-Sengstaken esophageal tamponade tube.

NEWS AND NOTICES

THE RESPONSIBILITIES OF THE MEDICAL PROFESSION IN THE USE OF X-RAYS AND OTHER IONIZING RADIATION

Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation

1. The United Nations General Assembly, being aware of the problems in public health that are created by the development of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radio-therapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

2. Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation in the detection, diagnosis and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

3. It is now accepted that the irradiation of human beings, and particularly of their germinal tissues, has certain undesirable effects. While many of the somatic effects of radiation may be reversible, germinal irradiation normally has an irreversible and therefore cumulative effect. Any irradiation of the germinal tissues, however slight, thus involves genetic damage which may be small but is nevertheless real. For somatic effects there may however be thresholds for any irreversible effects, although if so these thresholds may well be low.

4. The information so far available indicates that the human race is subjected to natural radiation,[1] as well as to artificial radiation due to its medical applications, to atomic industry and its effluents and to the radioactive fall-out from nuclear explosions. The Committee is aware of the potential hazards that such radiation involves, and it is collecting and examining information on these subjects.

[1] The radiation due to natural sources has been estimated to cause between 70 and 170 millirem of irradiation to the gonads per annum in most parts of certain countries in which it has been studied, although higher values are found locally in some areas. See the reports "The hazards to man of nuclear and allied radiations" published by the United Kingdom Medical Research Council in June 1956, in which also the millirem is defined; and from information submitted to the Committee.

5. The amount of radiation received by the population for medical purposes is now, in certain countries, the main source of artificial radiation and is probably about equal to that from all natural sources. Moreover, since it is given on medical advice, the medical profession exercises responsibility in its use.

6. The Committee appreciates fully the importance and value of the correct medical use of radiation, both in the diagnosis of a large number of conditions, in the treatment of many such diseases as cancer, in the early mass detection of conditions such as pulmonary tuberculosis, and in the extension of medical knowledge.

7. Moreover, it appreciates fully the contribution of the radiological profession, through the International Commission on Radiological Protection[2] in recommending maximum permissible levels of irradiation. As regards those whose occupation exposes them to radiation, the establishment of these levels depends on the view that there are doses which, according to present knowledge, do not cause any appreciable body injury in the irradiated individual; and also on the consideration that the number of people concerned is sufficiently small for the genetic repercussions upon the population as a whole to be slight. Whenever exposure of the whole population is involved, however, it is considered prudent to limit the dose of radiation received by germinal tissue from all artificial sources to an amount of the order of that received from the natural background radiation.

8. It appears most important therefore that medical irradiations of any form should be restricted to those which are of value and importance, either in investigation or in treatment, so that the irradiation of the population may be minimized without any impairment of the efficient medical use of radiation.

9. The Committee is consequently anxious to receive information through appropriate governmental channels as to the methods and the extent by which such economy in the medical use of radiation can be achieved, both by avoiding examinations which are not clearly indicated and by decreasing the exposure to radiation during examinations, particularly if the gonads, or the foetus during pregnancy lie in the direct beam of radiation. It seeks, in particular, to obtain information as to the reduction in radiation of the population which might be achieved by improvements in instrument design, by fuller training of personnel, by local shielding of the gonads, by choosing appropriately between radiography and fluoroscopy, and by better administrative arrangements to avoid unnecessary repetition of identical examinations.

10. The Committee also seeks the co-operation of the medical profession to make possible an estimate of the total radiation received by the germinal tissue of the population before and during the child-bearing age. It considers it to be essential that standardized methods of measurement, of types at present available, should be widely used to obtain this information and it emphasizes the

[2] See the report of the International Commission on Radiological Protection (published in the British Journal of Radiology—Supp. 6, of December 1954—in the *Journal français d'electro-radiologie*—No. 10, of October 1955—etc. and revised in 1956).

value of adequate records, maintained by those using radiation medically, by the dental profession, and by the responsible organizations in allowing such radiation exposure to be evaluated. The Committee is convinced that information of this type will make it possible to decrease the total medical irradiation of the population while preserving and increasing the true value of the medical uses of radiation.

THE GERONTOLOGICAL SOCIETY, INC.

Notice of Meeting and Call for Papers

The Tenth Annual Scientific Meeting of the Gerontological Society, Inc., will be held at the Cleveland Hotel, Cleveland, Ohio, October 31, and November 1 and 2, 1957.

For consideration by the Program Committee, abstracts of papers should be sent prior to July 1, 1957, to the Chairman of the appropriate Section listed below. Abstracts should be submitted in *triplicate*, *double-spaced*, and should include the title, author(s), and laboratory or institution of origin. The text of the abstract should be essentially the paper in miniature and should contain sufficient information for the Program Committee to judge its appropriateness for the various sections of the program. In general the abstract should include the purpose of the study, the methods, the nature and size of the sample of animals, subjects, or patients, and the results or conclusions. At the end of the abstract the author should indicate if he will present slides. Abstracts should not exceed 250 words; longer abstracts will be returned or edited to that length at the discretion of the Program Committee. Abstracts should be carefully checked by the authors and be "letter perfect" since galley proofs of abstracts will not be sent to the authors. If tabular matter is included in the abstract, costs in excess of 20 per cent of the cost of composition and printing of the abstract will be charged to the author. Orders for reprints of abstracts should be sent to the JOURNAL OF GERONTOLOGY, 660 South Kingshighway Blvd., St. Louis 10, Missouri, by September 1, 1957.

Program rules provide that each speaker be given 10 minutes for his presentation, followed by a 5-minute discussion period. In the Section on Clinical Medicine presentation time will be 15 minutes, followed by a 5-minute discussion period. No individual may present or be the senior author of more than one paper. Individuals may co-author more than one paper.

Biological Sciences: Dr. Albert I. Lansing, Department of Anatomy, University of Pittsburgh School of Medicine, Pittsburgh 13, Pennsylvania.

Clinical Medicine: Dr. Joseph T. Freeman, 1530 Locust Street, Philadelphia 2, Pennsylvania.

Psychological and Social Sciences: Dr. Wilma T. Donahue, University of Michigan, 1510 Rackham Building, Ann Arbor, Michigan.

Social Welfare: Miss Florence E. Vickery, San Francisco Senior Center, Polk and Beach Streets, San Francisco, California.

DR. JAMES E. BIRREN, *Program Chairman*
Section on Aging, National Institute of Mental Health,
Bethesda 14, Maryland